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CONTENTS OF PREVIOUS NUMBERS

JANUARY, 1923. NUMBER 1

The Carbon Dioxid and Oxygen Content of Stomach Gas in Normal Persons. Arthur D. Dunn, M.D., and Warren Thompson, M.D., Omaha.

Studies in the Chemotherapy of Bacterial Infections. II. The Chemotherapy of Experimental Localized Bacterial Infections with Special Reference to Pleuritis. John A. Kolmer, M.D., Philadelphia.

An Experimental and Clinical Study of Quinidin Sulphate. I. Experimental. Horace Marshall Korns, M.D., Cleveland.

An Experimental and Clinical Study of Quinidin Sulphate. II. Clinical. Horace Marshall Korns, M.D., Cleveland.

On the Technic of the Determination of the Velocity of the Arterial Pulse Wave. Christen Lundsgaard and Otto Beyerholm, Copenhagen, Denmark.

The Relation Between Ingested Fat and the Lipemia of Diabetes Mellitus. Phil L. Marsh, M.D., and H. G. Waller, M.D., Ann Arbor, Mich.

Defects in the Membranous Bones, Diabetes Insipidus and Exophthalmus, with Report of a Case. L. C. Grosh, M.D., and J. L. Stifel, M.D., Toledo, Ohio.

Orthopnea. Chester D. Christie, M.D., and Argyl J. Beams, M.D., Cleveland.

The Effect of Olive Oil and Gastric Function as Measured by Fractional Analysis. Bruce C. Lockwood, M.D., and Hasen G. Chamberlain, M.D., Detroit.

Study in Basal Metabolism in Dementia Praecox and Manic-Depressive Psychoses. Charles R. Gibbs, M.D., and Dorothea Lemcke, B.S., New York.

Hippuric Acid Synthesis as a Test of Renal Function. Sergius Morgulis, M.D., George P. Pratt, M.D., and Herman M. Johr, M.D., Omaha.

Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia. C. A. L. Binger, M.D.; A. B. Hastings, Ph.D., and J. M. Neill, Ph.D., New York.

FEBRUARY, 1923. NUMBER 2

Protein Feeding and High Blood Pressure. Solomon Strouse, M.D., and Sarah R. Kelman, M.D., Chicago.

Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects. H. C. Gram, M.D., and A. Norgaard, M.D., Copenhagen.

Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer. Leo L. Hardt, M.D., and Andrew B. Rivers, M.D., Rochester, Minn.

A Simple Immersion Electrode for Taking Clinical Electrocardiograms. Harold E. B. Pardee, M.D., New York.

Paroxysmal Ventricular Tachycardia: Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation. C. C. Wolferth, M.D., and Thomas M. McMillan, M.D., Philadelphia.

The Surgical Treatment of Angina Pectoris. Walter B. Coffey, M.D., and Philip King Brown, M.D., San Francisco.

Fatty Degeneration of the Heart. A. M. Master, M.D., New York.

Intrapericardial Rupture of Aortic Aneurysm in a Boy Sixteen Years of Age. DeWayne G. Richey, Pittsburgh.

Blood Sugar Standards. Part I. Normal and Diabetic Persons. Horace Gray, M.D., Boston.

Blood Sugar Standards. Part II. In Conditions Neither Normal nor Diabetic. Horace Gray, M.D., Boston.

Intracutaneous Reactions in Lobar Pneumonia to Pneumotoxin. (A Reply to Dr. George H. Bigelow.) Charles Weiss, Ph.D., and John A. Kolmer, M.D., Philadelphia.

Some Observations on the Value of the Index and Angle of Bordet-Vaquez in Cardiac Examination. David S. Dann, M.D., Boston.

Pathologic Physiology of Polycythemia Vera. Raphael Isaacs, M.D., Cincinnati.

The Etiology of Acute Intestinal Intoxication in Infants. Gladys L. Boyd, M.B., Toronto.

Book Review.

MARCH, 1923. NUMBER 3

Further Observations on the Roentgen-Ray Treatment of Toxic Goiter. J. H. Means, M.D., and G. W. Holmes, M.D., Boston.

The Correlation of Vital Capacity with Stem Height. William Lester Rogers, San Francisco.

A Clinical Report on the Use of Quinidin Sulphate. L. E. Viko, M.D.; H. M. Marvin, M.D., and Paul D. White, M.D., Boston.

Enlargement of Hemal Nodes. Max Lederer, M.D., Brooklyn, N. Y.

Studies on the Detoxification of Cyanids: I. Some Factors Influencing the Detoxification of Cyanids in Health and Disease. Meyer Bodansky, M.A., and Moise D. Levy, M.D., Galveston, Tex.

Studies of the Blood Gases in a Case of Paroxysmal Tachycardia. Edward P. Carter, M.D., and Harold J. Stewart, M.D., Baltimore.

Observations of the Cardiovascular System in Thyroid Disease. W. J. Kerr, M.D., and George C. Hensel, M.D., San Francisco.

A Case of Rheumatic Fever with Cerebral Symptoms Simulating Encephalitis Lethargica. Lewis Fox Frissell, M.D., New York.

Gravimetric Estimation of Phosphates of the Blood: Phosphates in Nephritis. William J. Fetter, M.D., Pittsburgh.

The Increase of Certain Vagal Effects with Increased Age. N. C. Gilbert, M.D., Chicago.

Studies of Exophthalmic Goiter and the Involuntary Nervous System. Leo Kessel, M.D.; Charles C. Lieb, M.D., and Harold T. Hyman, M.D. III. A Study of Fifty Consecutive Cases of Exophthalmic Goiter. Leo Kessel, M.D.; Harold T. Hyman, M.D., and Herman Lande, M.D., New York.

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FURTHER OBSERVATIONS ON THE USE OF A HIGH FAT DIET IN THE TREATMENT OF DIABETES MELLITUS*

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INTRODUCTION

During the early part of this century it was customary to use a very liberal protein fat diet in the treatment of diabetes mellitus. This type of diet was characterized by its high protein content, its relative poverty of carbohydrate and its high caloric value. Mild diabetics did quite well on such a regimen, but the more severely ill patients did not tolerate it without glycosuria and the persistence of diabetic symptoms, and, as pointed out by Joslin, coma was so common that the percentage of deaths in hospitals was greater than in homes. It was necessary to conceive of a mysterious "spontaneous downward progress" to explain the constant loss of tolerance in these cases, and the majority of physicians felt that treatment of the severe cases was a waste of time and energy. This type of diet is not by any means without its supporters today, and it is surprising to note how many patients coming to the University Hospital have had their carbohydrate intake strictly limited, but have been allowed to eat as much other food as they wanted, chiefly in the form of meat, eggs and patent diabetic foods.

In 1914, Allen introduced the principle of undernutrition with the object of relieving the strain on the pancreas, and of stopping the spontaneous progress of the disease. In more or less modified form this principle has since then been used widely in the treatment of diabetes mellitus. Under the leadership of Joslin it has been applied in practice by beginning treatment with fasting, which may or may not be preceded by three or four days of observation and increasing curtailment of the diet. After the period of fasting, the diet is built up step by step until the patient is receiving a ration well within his carbohydrate tolerance, in which neither fat nor protein nor carbohydrate furnishes a disproportion of the calories. It is especially insisted that the fat content of the diet be small. The final diet is one which may not and often does not satisfy the caloric requirement of the

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organism. In the more severe cases a marked degree of undernutrition results, with weakness, depression and chronic invalidism, and inanition appears on the records as a cause of death.

There is abundant evidence that overfeeding and large gains in weight are detrimental to the diabetic. On the other hand, a number of very apparent evils are associated with severe undernutrition. It seemed to us possible that a diet could be arranged, which, while still controlling the diabetic state, might avoid the evils of the two extremes. With the basic principles of the metabolism of the three foodstuffs in mind, it is possible, in theory, to construct such a diet by deriving the major portion of the calories from fat. Before advocating the use of such a diet, however, it was necessary to demonstrate that the use of the much feared fat is, in fact, safe.

In a previous communication [1] we reported that in seventy-three consecutive cases this type of diet was strikingly successful in controlling glycosuria, avoiding acidosis, maintaining nitrogen balance and permitting ordinary activity on the part of the patient. In a second communication [2] we showed the beneficial effect of these diets on hyperglycemia. We emphasized the fact, however, that our experience with this diet was brief in relation to the chronicity of the disease, and we were, therefore, very guarded in our statements of the probable results of adherence to it over a long period of time. Nearly two years have elapsed since our first communication, and a statement of the present status of some of our earlier patients and of additional observations on some of our more recent ones cannot fail to be instructive. It is the purpose of this paper to present our experience with the high fat diet in the light of our longer study, and to discuss certain cases which offer striking examples of fundamental principles in the dietetic management of diabetes mellitus.

The diets used are essentially the same as those previously described; more day to day variation in the composition of the diets is allowed than at first in order to relieve the monotony of the menus, but in principle the treatment is the same as that discussed in our first paper. When an adult diabetic patient is admitted to the ward, he is automatically and without preparation given a daily diet which contains protein, from 15 to 20 gm., fat, from 85 to 95 gm., carbohydrate, from 10 to 12 gm. Because of the smaller body mass of children, their total calories are correspondingly reduced, but the proportions of the food stuffs used are

1. Newburgh, L. H., and Marsh, P. L.: Use of a High Fat Diet in the Treatment of Diabetes Mellitus: First Paper, Arch. Int. Med. **26**:647 (Nov.) 1920.

2. Newburgh, L. H., and Marsh, P. L.: Use of a High Fat Diet in the Treatment of Diabetes Mellitus: Second Paper: Blood Sugar, Arch. Int. Med. **27**:699 (May) 1921.

the same. No preliminary fast or gradation of diets has been used, and the high fat diet is served from the first meal in the hospital. After the adult patient is desugarized, his diet is increased by steps until he is receiving 0.67 gm. protein and from 30 to 40 calories per kilogram of body weight, or sometimes a little more than this. In children more protein and more calories per kilogram of body weight are allowed, in accordance with principles that will be discussed later, but the same plan of distribution of the food stuffs is used for children as for adults. In no case in this series has the daily carbohydrate allowance been greater than 35 gm. After the patient has been found to tolerate a maintenance diet of this type during several days in the ward, he is discharged with instructions to adhere to it rigidly.

RESULTS

Six major considerations enter into a discussion of the dietetic treatment of diabetes mellitus, namely: (1) glycosuria; (2) acidosis; (3) nitrogen balance; (4) lipemia; (5) the general condition of the patient, and (6) the effect of treatment on glucose tolerance and expectation of life.

1. *Glycosuria.*[3]—Since the first aim of dietetic treatment of diabetes is the avoidance of glycosuria with the associated complications and loss of tolerance, the prime requisite of the diet is that it keep the urine of the diabetic patient free from sugar. We have had the opportunity since the inception of this treatment of observing 190 diabetics. Of these, six entered the hospital in coma or in extremis from other causes, and died either before treatment could be inaugurated or before it could significantly affect the metabolism (Table 12). Eight others remained but a few days, and left against our advice when they found that we had nothing to offer except diet in place of the curative drug or operation that they had expected (Table 13). None of the remaining 176 diabetic patients failed to become sugar free, and all of these were discharged without glycosuria on a maintenance diet. While none of them were "total diabetics," many were of the very severe grades, and a large number of them were young. In Table 1 are presented the ages of onset of this group by decades. Appended is part of the record of one of the younger patients (Case 1).

CASE 1 (22-610).—*History.*—A boy, 3 years of age (born Nov. 5, 1918) entered the hospital March 6, 1922, with diabetes that had appeared abruptly in June, 1921, with polyuria and polydipsia. His father's brother has diabetes. There was nothing of importance in his past history. The diagnosis of diabetes was made immediately, and he was taken into a hospital in his home city for treatment, which was instituted with a fast. Little information could be

3. No cases diagnosed renal glycosuria are included in this study.

obtained concerning this period of treatment, except that after a few days of fasting his condition seemed very serious and his mother states that he was on the verge of coma. He was given food, but the mother does not know the quantities. His diet was gradually increased until he was receiving protein, 40 gm., fat, 33 gm., carbohydrate 25 gm. and 560 calories. On this diet he had constant glycosuria and a heavy ferric chlorid reaction in his urine. During the two months before admission he had not been sugar free at any time. At the beginning of his illness he weighed 32 pounds and at admission 28 pounds.

Physical Examination.—This showed nothing of importance.

Comment.—Part of his record is presented in Table 2. It will be noted that his urine became sugar free on the eleventh day and the ferric chlorid reaction was negative at the same time. The gain in body weight during the first few days was probably due to changes in the fluid content of his body. Nitrogen balance was established on a diet containing 30 gm. protein, 75 gm. fat, and 12 gm. carbohydrate. At present, he is receiving 30 gm. protein, 115 gm. fat, 17 gm. carbohydrate and 1,225 calories, which allows him 93 calories per kilogram of body weight. He is slowly gaining in weight and has added one-fourth inch to his height.

TABLE 1.—AGE AT ONSET BY DECADES OF AUTHORS' GROUP. FOR COMPARISON A SIMILAR TABLE OF A GROUP OF JOSLIN'S PATIENTS IS ADDED

Age at Onset	Authors' Series			Joslin's[4]	
	Number	Per Cent.		Per Cent.	
0-10	6	3.2		5.3	
11-20	14	7.4	40.6	8.7	38.6
21-30	24	12.6		10.8	
31-40	33	17.4		13.8	
41-50	37	19.5		24.7	
51-60	56	29.5		23.0	
61-70	17	8.9		10.1	
71-80	3	1.6		3.0	

In some cases we have had the opportunity of contrasting in the same patient the results of our diets with the results of other methods of treatment. A number of the patients in this series who had been treated unsuccessfully by high protein diets before coming to us became aglycosuric on our diets. That this would occur is only to be expected, but it must be mentioned because of the widespread use of these high protein diets.

Of still greater interest is the group in which fasting and severe undernutrition have failed to control the glycosuria. The records of two patients (Cases 2 and 3) show clearly that some diabetics who could not be made sugar free by starvation may be made so by a high fat diet yielding about 950 calories.

CASE 2 (21-321).—*History.*—An American farmer, 28 years of age, entered the hospital March 1, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes, except that a 4-year old son of the patient has had an occasional glycosuria. There was nothing of importance in his past history. Polyuria, polydipsia and polyphagia developed in August, 1914, when

4. Joslin, E. P.: Diabetes Mellitus, Oxford Medicine, Oxford University Press **4**:153, 1921.

the patient was 21 years old. During the following three months his weight fell from 160 to 113 pounds. Treatment was not started until January, 1915. Four days of complete fasting, followed by several days during which he was allowed green vegetables, and two or three more days of fasting, a total of ten days, rendered his urine sugar free. He was discharged on a diet which allowed him considerable freedom in the kinds of the food stuffs that he ate but which was very much restricted in total calories. During the following two years he felt fairly well most of the time, although he had sugar in his urine frequently. Between the Spring of 1916 and March, 1921, he was free from sugar at no time in spite of the fact that he was fasted on five occasions for periods of from four to ten days. During the month preceding his admission to our ward he suffered from epigastric distress, "heart burn" and nausea. His symptoms were sufficiently severe to make his home physician suspect peptic ulcer. His vision had failed and he was badly constipated.

TABLE 2.—Part of Record of a Three Year Old Diabetic (Case 1)

	Diet				Urine			
Date, 1922	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Nitrogen, Gm.	Weight, Lbs.
3/ 8*	14.3	45.0	4.9	480	++++	++++	....	28
3/ 9	12.2	41.5	6.6	450	5.4	++++	....	....
3/10	13.3	44.0	5.7	470	4.1	++++	....	....
3/11	12.3	43.0	4.8	465	5.4	+++	....	....
3/12	14.4	47.0	6.4	506	3.0	+++	....	....
3/13	16.5	57.6	8.2	615	Trace	++	....	....
3/14	13.1	59.1	11.3	630	7.3	++	....	....
3/15	13.0	54.0	3.8	555	5.1	++	....	....
3/16	13.1	47.1	6.4	501	6.2	+++	....	30.5
3/17	9.8	40.7	7.2	435	2.3	+++	....	....
3/18	9.7	40.1	6.4	425	0	0	....	....
3/19	10.8	43.3	7.5	465	0	0	....	....
3/20	10.8	43.3	7.1	460	0	0	....	....
3/21	14.8	46.2	7.1	505	0	0	....	....
3/22	14.8	46.2	7.1	505	0	0	....	30.5
3/23	13.2	40.0	7.1	440	0	0	....	....
3/23 to 3/29	20.0	45.0	7.0	515	0	0	....	29.0
3/30 to 4/ 5	25.0	55.0	12.0	645	0	0	9.29	29.0
4/ 6 to 4/ 9	30.0	55.0	12.0	665	0	0	7.52	30.0
4/10 to 4/12†	30.0	65.0	12.0	755	0	0	7.82	30 5
4/13	30.0	75.0	12.0	845	0	0	....	30.0
4/14	Dietetic error				3.7	0	....	....
4/15 to 4/19	30.0	55.0	12.0	665	0	0	....	28
4/20 to 5/19	30.0	65.0	12.0	755	0	0	5.21	27
5/20 to 6/ 4	30.0	75.0	12.0	845	0	0	4.48	26.5
6/ 5 to 6/12	30.0	85.0	17.0	955	0	0	3.87	27
6/13 to 6/15	30.0	96.0	17.0	1,045	0	0	3.59	27
6/16 to 6/20	30.0	106.0	17.0	1,135	0	0	....	28
6/21 to 7/20	30.0	115.0	17.0	1,225‡	0	0	....	29

* Bloor fat, 1.13 per cent.
† Bloor fat, 0.89 per cent.
‡ 93 calories per kilogram of body weight.

Physical Examination.—On examination it was noted that he was decidedly stuporous and went to sleep while his blood was being taken for the laboratory examinations. Later, he could not remember anything that had happened during the first day he was in the hospital. His breath had a decided acetone odor. His right knee jerk could be obtained only on reenforcement and his left could not be obtained at all. His urine contained a trace of albumin, reduced Fehling's solution and gave a heavy reaction with ferric chlorid. His blood sugar was 0.38 per cent. and the carbon dioxid combining power of the blood plasma by the Van Slyke method was 37 volume per cent.

Comment.—The day to day record of his first two or three weeks, with a summary of the following few weeks in the hospital is presented in Table 3. It will be seen that his urine became sugar free on the twelfth day in the hospital.

Case 3 (21-1993).—*History.*—A Russian housewife, 25 years of age, entered the hospital July 13, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes and her past history was of no importance. In March, 1920, she had severe attacks of cramps in the legs associated with excessive thirst and polyuria. Other symptoms were failing vision, obstinate constipation and progressive loss of weight. She had no systematic treatment until August 13, 1920, at which time she was fasted for five days and her urine became sugar free. Her diet was increased until she was receiving, protein, 50 gm.; fat, 20 gm.; carbohydrate, 30 gm.; about 500 calories with one fast day each week. From this time until July 1, 1921, she adhered rigidly to this diet, which was prepared by a trained dietitian, with the exception of a short period in January, 1921, when she was allowed one or two slices of bacon a day in addition. At no time during this whole period, except on the last day of her initial fast, was her urine free from sugar; this statement was confirmed by

TABLE 3.—Part of Record of Patient (Case 2) Who Had Failed to Become Sugar Free During Several Periods of Fasting

	Diet				Urine			Blood		
Date, 1921	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Amount, C.c.	Glucose, Gm.	Diacetic	Sugar, %	CO_2, Vol., %	Weight, Lbs.
3/ 2	19.1	95.4	14.2	990	1,250	43.8	++++	0.38	37	133
3/ 3	22.2	69.0	13.4	865	2,150	56.6	++++	....	..	...
3/ 4	21.7	94.4	14.8	995	1,650	25.1	++	....	..	132
3/ 5	20.8	89.9	13.4	940	2,170	18.1	++	....	..	...
3/ 6	21.2	89.0	13.4	935	1,925	17.5	++++	0.27	51	134
3/ 7	21.2	89.0	13.4	935	2,350	20.2	+++	....	..	...
3/ 8	20.5	92.4	14.6	970	2,355	17.5	+++	....	..	133
3/ 9	19.1	95.4	14.2	990	2,100	11.9	+++	....	..	134
3/10	15.3	99.5	11.0	1,000	1,500	7.8	+++	....	..	134
3/11	14.9	101.0	10.5	1,015	1,640	5.6	+++	....	..	...
3/12	15.2	100.1	11.0	1,005	2,335	0	+++	....	..	136
3/13	15.4	100.0	11.3	1,005	1,760	Trace	++	0.13	64	...
3/14	15.4	100.0	11.0	1,005	1,895	0	+++	....	..	134
3/15	15.4	100.0	11.0	1,005	3,150	0	+++	....	..	...
3/16	15.4	100.1	11.1	1,005	2,215	0	++	0.13	65	132
3/17	24.8	149.6	15.2	1,505	1,565	0	+	....	..	...
3/18	26.1	151.1	15.3	1,525	4,370	0	Trace	....	..	135
3/19	25.2	150.7	14.2	1,515	3,270	0	Trace	....	..	...
3/20	26.1	149.7	14.6	1,510	3,190	0	0	....	..	132
3/21	24.8	149.6	15.2	1,505	2,200	0	0	....	75	...
3/21 to 3/30	43.0	180.0	15.0	1,850	.....	0	0	....	66	130
3/31 to 4/4	43.0	200.0	15.0	2,030	.....	0	0	....	65	...
4/5 to 4/20	43.0	220.0	11.0	2,200	.....	0	0	....	65	...

her home physician. July 1, 1921, fasting was again started, and this time four days of complete fasting, followed by five days in which she was allowed "a few" 5 per cent. vegetables, failed to render her urine sugar free, and she refused to fast longer. During the few days before she came to us she adhered to the original 500 calory diet.

In February, 1920, she weighed 145 pounds.

Physical Examination.—The patient was an unusually intelligent woman, 59 inches tall, weighing 100 pounds, with no important abnormalities aside from her laboratory examinations. Part of her record is presented in Table 4.

Comment.—She was discharged from the hospital on a diet which gave her about 1,400 calories daily, and she has remained sugar free up to the present time, a period of nearly one year.

2. *Acidosis.*—A diabetic diet, to be successful, must not precipitate acidosis, and should, in those cases in which acidosis is present, be attended by relief of the acidosis. Since the demonstration of the derivation of acetone bodies from fat, there has developed a wide-spread

fear of the use of fat in the treatment of diabetes. It was, therefore, very important that we study with the greatest care the relation between the amount of fat in our diet and acidosis.

Of the 190 patients with diabetes whom we have had under our care since we have used the high fat diets, six gave us no information as to its effect on acidosis. Four of the latter entered the hospital in diabetic coma, the fifth in coma from sepsis, the sixth in extremis following a therapeutic fast, and none of them were treated dietetically. The other 184 patients include eight who left the hospital against our advice within a week and before they were sugar free, but who were, nevertheless, on the diet during the few days they were in the hospital. In none of these 184 cases did an important acidosis develop. It should

TABLE 4.—Record from Case 3, in Which Fasting and Severe Undernutrition Had Failed to Keep Urine Sugar Free

Date, 1921	Average Diet				Urine Sugar, Gm.	Ferric Chlorid Reaction	Body Weight, Lbs.
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories			
7/13	....	.....	....	.....	25.5	++++	100
7/14	....	.....	....	.....	16.3	+++	...
7/15	....	.....	....	.....	8.8	+++	...
7/16	20.0	85.8	13.1	905	4.0	++	...
7/17	....	.....	....	.....	0	0	99
7/18	....	.....	....	.....	0	0	...
7/19	....	.....	....	.....	0	0	...
7/20	....	.....	....	.....	0	0	95
7/21	....	.. ..	....	.....	0	0	...
7/22	....	.....	....	.....	0	0	...
7/23	....	.....	....	.....	0	0	...
7/24	28.4	137.4	20.8	1,435	0	0	...
7/25	....	.....	....	.....	0	0	96
7/26	....	.....	....	.....	0	0	...
7/27	....	.....	....	.....	0	0	...

be pointed out, again, that every one of these patients, regardless of age, severity of the diabetes or degree of acidosis was placed on the diet at entrance. Early in the use of the treatment a few patients were given sodium bicarbonate, but this has not been used in any case since July 1, 1920, since which date much more than one half of this series of cases have been treated. A few examples are cited showing the absence of acidosis on the treatment.

Case 4 (21-678).—*History.*—An American clerk, 19 years of age, entered the hospital March 24, 1921, complaining of the usual diabetic symptoms. There was no history of diabetes in the family and nothing of importance in his past history. The disease had developed abruptly fifteen months before, and during the first three months he lost 30 pounds in weight. In spite of severe restriction in his diet there was no improvement in his symptoms. Twelve days before he came to us he was fasted for seven days but he did not know whether he became sugar free. There had been some numbness of his feet and for two months he had had boils on his legs.

Physical Examination.—Edivence of advanced bilateral pulmonary tuberculosis was found and this complication was confirmed by the roentgenogram and the sputum examination. Part of his data are presented in Table 5.

CASE 5 (21-276).—*History.*—An American farmer, 22 years of age, entered the hospital Feb. 7, 1921, complaining of polyuria, weakness and loss of weight. A brother died of diabetes at 17. The past history is of no importance. His best weight was 164 pounds just before the onset of his diabetes; his weight at admission was 127. His symptoms appeared abruptly in August, 1920, and the diagnosis was made immediately by his physician. His diet was moderately restricted and he continued to lose weight and strength.

TABLE 5.—PART OF RECORD OF CASE 4, SHOWING ABSENCE OF ACIDOSIS IN A YOUNG DIABETIC WITH PULMONARY TUBERCULOSIS

Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Sugar	Ferric Chlorid	Plasma CO_2, Volume per Cent.	Blood Sugar, per Cent.
3/24*	.....	.....	.....	.....	+++	++	61.4	0.33
3/25	21.7	99.4	14.8	995	+	+	.....	.....
3/26	29.1	129.1	21.1	1,320	0	0	.....	.....
3/27	19.1	95.4	14.2	990	0	0	.....	.....
3/28	21.2	85.9	13.4	910	0	0	61.7	0.23
3/29	20.2	92.4	14.6	960	0	0	.....	.....
3/30	30.0	147.1	14.2	1,500	0	0	.....	.....
3/31	31.7	151.9	15.5	1,535	0	0	.....	.....
4/ 1	29.9	149.4	14.8	1,525	0	0	.....	.....
4/ 2	30.2	149.3	14.9	1,525	0	0	.....	.....
4/ 3	28.8	152.4	14.8	1,545	0	0	.....	.....
4/ 4	30.3	152.0	14.9	1,550	0	0	63.6	0.16
4/ 5	31.1	180.7	14.2	1,800	0	0	.....	.....
4/ 6	30.0	179.3	14.2	1,785	0	0	.....	.....
4/ 7	29.1	178.2	15.0	1,765	0	0	.....	.....
4/ 8	29.7	180.2	15.3	1,800	0	0	61.7	0.16

* Admitted in evening.

TABLE 6.—SHOWING ABSENCE OF ACIDOSIS IN YOUNG DIABETIC ON HIGH FAT DIET (CASE 5)

	Diet				Urine			
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Ferric Chlorid	Blood Sugar, per Cent.	Plasma CO_2, per Cent.
2/ 8	18.9	91.2	14.2	955	++++	+++	0.26	62.0
2/ 9	20.6	87.6	14.6	940	24.7	++++	0.18	.....
2/10	20.4	84.2	12.8	890	13.5	++++	.....	.....
2/11	21.1	93.9	14.9	990	0	++++	.....	.....
2/12	20.5	88.7	14.4	890	0	++++	.....	.....
2/13	21.0	92.0	15.0	970	0	++	.....	.....
2/14	18.2	91.2	14.3	950	0	Trace	0.20	.....
2/15	20.6	87.6	14.6	940	0	Trace	.....	61.4
2/16	21.5	80.4	14.6	870	0	0	.....	.....
2/17	21.3	77.7	12.8	845	0	0	.....	.....
2/18	20.2	87.3	14.1	935	0	0	.....	56.5
2/19	20.5	83.7	14.4	890	0	0	.....	.....
2/20	20.6	87.6	14.6	940	0	0	.....	.....
2/21	21.3	77.7	12.8	845	0	0	.....	.....
2/22	40.6	153.2	20.6	1,625	0	0	.....	.....
2/23	39.3	156.5	19.6	1,645	0	0	0.10	55.7
2/24	40.2	153.4	20.3	1,625	0	0	.....	.....
2/25 to 3/ 1	40.2	152.6	20.6	1,615	0	0	0.13	62.6
3/ 2 to 3/ 7	40.8	152.1	20.6	1,615	0	0	0.12	58.9
3/ 8 to 3/12	40.0	180.3	20.4	1,865	0	0	.....	.....
3/13 to 3/17	40.0	179.4	20.6	1,855	0	0	.....	65.3
3/18 to 3/20	40.5	200.2	25.0	2,065	0	0	.....	59.8
3/21 to 3/29	40.9	200.2	25.0	2,070	0	0	0.08	65.3
3/30 to 4/ 4	40.6	200.2	25.0	2,065	0	0	0.10	60.7
4/ 5 to 4/ 8	43.1	229.1	25.6	2,340	0	0	.....	61.7

Physical Examination.—Except for septic tonsils, his physical examination was negative. Part of his record is presented in Table 6.

CASE 6 (21-1021).—*History.*—An American farmer, aged 45 years, entered the hospital March 19, 1921, complaining of polyuria and weakness. His mother died at the age of 51 of diabetes mellitus. He had had frequent

urinalyses because of his mother's diabetes, but no sugar was found until December, 1920, about two weeks after the onset of polyuria and weakness. A "carbohydrate free" diet failed to render his urine sugar free, his physician stating that the urine always contained from 3 to 6 per cent. of sugar.

Physical Examination.—Except for pyorrhea alveolaris, his physical examination was negative. His average weight was 155 pounds; at admission he weighed 130 pounds. Part of his record is presented in Table 7.

Not only does acidosis not develop in patients who are living on this diet, but it is a fact that all our patients showing at admission an acidosis short of coma rather promptly lost their acidosis while taking the high fat diet. One such case has already been mentioned in our first communication. Three other striking examples are cited from our more recent experience.

TABLE 7.—SHOWING ABSENCE OF ACIDOSIS ON HIGH FAT DIET (CASE 6)

Date, 1921	Average Diet				Urine		Plasma CO_2, Volume per Cent.
	Protein, Gm.	Fat, Gm.	Carbohydrate Gm	Calories	Sugar	Diacetic	
4/ 7	18	85	15	900	++++	++++	64.5
4/ 8	..	...	..	.....	++++	++++	....
4/ 9	..	...	..	.....	+++	++++	....
4/10	..	...	..	.....	+++	+++	....
4/11	..	...	..	.....	++	+++	....
4/12	..	...	..	.....	+	+	....
4/13	..	...	..	.....	0	+	....
4/14	..	...	..	.....	0	0	....
4/15	..	...	..	.....	0	0	....
4/16	..	...	..	.....	0	0	....
4/17	..	...	..	.....	0	0	....
4/18	..	...	..	.....	0	0	....
4/19	..	...	..	.....	0	0	65.5
4/20	..	...	..	.....	0	0	....
4/21	..	...	..	.....	0	0	....
4/22	..	...	..	.....	0	0	....
4/23	98	165	30	1,710	0	0	....
4/24	..	...	..	.....	0	0	....
4/25	..	...	..	.....	0	0	....
4/26	..	...	..	.....	0	0	55.1

Reference to the record of one patient (Case 2) and to Table 3 will show that he entered the hospital with a severe acidosis, which disappeared promptly on a high fat diet.

CASE 7 (22-2159).—*History.*—An American painter, 34 years of age, entered the hospital July 6, 1922, with a diabetes which had appeared abruptly in December, 1920, with polydipsia, polyuria and progressively increasing weakness. Three days of fasting rendered his urine sugar free and he was finally able to tolerate a fairly liberal diet. About eight weeks previous to admission he had a lower third molar extracted; infection ensued. There was an immediate return of glycosuria which he was unable to control. For the two weeks before he came to the hospital his diet had not been limited and he had become progressively more drowsy until at admission he was semicomatose. His weight had fallen from an average of 140 pounds to 90 pounds; his entrance weight was 103 pounds.

Physical Examination.—He was very stuporous and there was hyperpnea of the Kussmaul type. The patellar and Achilles reflexes could not be elicited. His skin had a lemon yellow cast, and numerous xanthomatous lesions were

scattered over his body. At the site of the tooth extraction in the lower right jaw there was evidence of osteomyelitis. His hemoglobin was 66 per cent. with 3,210,000 red blood cells and without leukocytosis. His blood plasma was creamy.

Comment.—The osteomyelitic lesion in the jaw was curetted and he was started on the routine diet. Fluids were forced during the first few days in the ward. In Table 8 will be found data of this period of treatment. There was a rapid improvement in the acidosis, as shown by the disappearance of acidosis, as well as by the laboratory findings. A moderate edema, present at entrance, increased rapidly and explains the great gain in weight.

Case 8 (21-1392).—*History.*—An American merchant, 35 years of age, entered the hospital May 18, 1921, complaining of loss of weight, weakness, polyuria and polydipsia. His symptoms developed abruptly in January, 1918, when he was 32 years of age. Glycosuria was found, and he became sugar free on a rather liberal diet. After a few weeks he was advised to return to a normal diet; symptoms and glycosuria promptly reappeared. He again became sugar free on the liberal diet and adhered to it about a year. During

TABLE 8.—Part of Record of Case 7. Rapid Disappearance of Severe Acidosis on High Fat Diet

	Diet				Urine		Blood			
Date, 1922	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Diacetic	Sugar, per Cent.	CO_2, Vol. per Cent.	Fat, per Cent.	Weight, Lbs.
7/ 7	21.7	85.0	12.6	900	50.3	++++	0.53	34	7.6	103
7/ 8	21.5	86.8	13.3	910	56.2	++++	....	38	...	100
7/ 9	21.0	86.5	13.2	925	29.4	++	....	..	...	101.5
7/10	21.5	86.6	14.1	935	41.4	++	....	64	...	108
7/11	20.4	98.6	13.5	980	17.5	+	....	..	...	115.5
7/12	21.3	88.7	13.0	930	11.1	+	....	..	2.8	116.0
7/13	20.1	96.7	13.0	975	11.4	0	....	..	...	117.0
7/14	21.7	87.1	12.6	920	Trace	0	....	..	...	116.5
7/15	21.0	86.6	13.2	910	4.0	0	....	..	...	117.5
7/16	21.5	85.8	13.3	910	0	0	0.20	..	1.69	117.0
7/17	21.7	84.0	14.1	900	0	0	....	72	...	119.0

the following year he increased his food intake and frequently found sugar in his urine. During this second year of his diabetes he had frequent night sweats, with one attack of pain in the lower left chest lasting some weeks. In February, 1920, he had influenza, and during the next few months his weakness progressively increased. In the fall of that year he spent four weeks in a sanatorium, and was discharged on a diet that was liberal, including a large quantity of gluten bread. From that time he gradually went down hill, and since February, 1921, he had not been able to work. During the course of the diabetes his weight had fallen from 120 to 85 pounds.

Physical Examination.—Abnormalities in both pulmonary apices were discovered but no sputum could be obtained.

Comment.—He was discharged from the hospital June 30, 1921, on a diet which gave him about 30 gm. protein, 160 gm. fat and 20 gm. carbohydrate. He did very well, working every day and remaining sugar free until September, 1921, when he developed glycosuria during an extended trip away from home. He returned to the hospital, was sugar free in fourteen days and was discharged on the same diet as previously. He has been able to do his work regularly since that time and is feeling well. Part of his record is presented in Table 9.

It should be noted that five of our 190 patients died in the hospital in coma. Four of these entered the hospital in coma and died without

dietetic treatment. In one of these cases, the coma was not accompanied by the usual signs of diabetic coma and at necropsy adenoma of the pituitary gland was found. The fifth patient, whose diabetes had been brought under control and who was not showing an acidosis, broke diet and developed a severe acidosis and from this time went progressively down hill, dying in coma. None of these deaths can be attributed to the effect of the diet.

3. *Nitrogen Balance.*—A diet to be satisfactory in the treatment of a chronic disease must be constructed so that it will maintain nitrogen balance. In a previous communication [5] it was shown that in the diabetic, as in a normal person, 0.66 gm. protein per kilogram of body weight is sufficient for this purpose, provided the total caloric intake is great enough to supply the metabolic needs of the organism. By

TABLE 9.—SHOWING RELIEF OF MODERATE ACIDOSIS BY HIGH FAT DIET (CASE 8)

	Diet				Urine		CO_2 Combining Power	
Date, 1921	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Glucose, Gm.	Ferric Chlorid	Blood Plasma, Vol. per Cent.	Weight, Lbs.
5/19	18.9	80.8	13.9	860	++++	++++	44.7	84.5
5/20	21.7	94.4	14.8	995	20.0	++++	....	....
5/21	20.4	83.3	11.8	875	18.4	++++	....	85.0
5/22	19.0	95.4	14.2	990	++++	++++	....	....
5/23	20.9	110.4	15.0	1,125	13.8	++++	....	....
5/24	20.8	89.9	13.4	945	12.3	++++	....	....
5/25	19.4	92.3	14.2	965	10.3	++++	....	....
5/26	21.2	85.9	13.4	910	+++	++++	....	....
5/27	21.9	94.4	14.8	995	++	++++	....	....
5/28	20.8	89.9	13.4	945	Trace	++	....	88.9
5/29	20.9	85.2	12.4	940	0	++	....	....
5/30	19.1	90.4	14.2	900	0	0	....	....
5/31	15.2	88.2	12.5	905	0	+	....	....
6/ 1	28.0	156.8	21.3	1,600	0	Trace	62.5	90.0
6/ 2	29.7	147.1	20.9	1,525	0	0	....	....

using relatively large quantities of fat, we have been able to satisfy the total caloric requirement of the patient without producing glycosuria and to maintain nitrogen balance on the small quantities of protein that we have allowed. The table published in the communication referred to is here reproduced (Table 10).

4. *Lipemia.*—A frequent accompaniment of the diabetic state is an increase in the amount of lipoid substances in the blood. While the true significance of this phenomenon is not known, it is at all events a departure from the normal, and its increase or its persistence during treatment is considered undesirable. It has been shown in another communication [6] from this clinic that (1) hyperlipoidemia is not produced by the high fat diet in those patients in whom it is not present

5. Marsh, P. L.; Newburgh, L. H., and Holly, L. E.: The Nitrogen Requirement for Maintenance in Diabetes Mellitus, Arch. Int. Med. **29**:97 (Jan.) 1922.

6. Marsh, P. L., and Waller, H. G.: Arch. Int. Med., to be published.

at entrance, and (*2*) an existing hyperlipoidemia, even of high degree, gradually falls until it has approximated or reached the normal level. It is, therefore, apparent that a high fat diet does not cause a hyperlipoidemia.

5. *General Condition of the Patient.*—Weakness and incapacitation are unavoidable evils resulting from fasting and undernutrition, and the diabetic is not exempt from these ill effects. It was with the hope of avoiding these disadvantages that we undertook an investigation of the use of fat for the purpose of supplying energy to the patient. The desugarization period and the long period of after treatment will be considered separately.

The initial period of fasting is very poorly borne by many of the more debilitated diabetics. When the fasting is continued for a week or more, the resulting exhaustion may be extreme. For example,

TABLE 10.—Diets on Which Nitrogen Balance Was Established in Twelve Patients with Diabetes Mellitus

Case No.	Age, Years	Weight, Kg.	Protein, Gm.	Fat, Gm.	Carbohydrate Gm.	Calories	Nitrogen, Gm.	Protein, per Kg., Gm.	Calories per Kg.	Per Cent. of Total Calories as Carbohydrate
1	56	63	34.3	168.4	6.9	1,680	5.49	0.54	27	1.6
2	68	66	39.3	231.4	12.8	2,295	6.27	0.59	35	2.3
3	37	60	54.1	240.1	13.4	2,430	8.66	0.90	41	2.2
4	18	42	28.5	162.8	9.9	1,615	4.49	0.68	38	2.4
5	21	50	37.8	163.6	8.2	1,650	6.05	0.75	33	1.9
6	49	70	65.0	197.0	9.9	2,065	10.04	0.93	30	1.9
7	22	59	33.5	150.1	25.4	1,585	5.36	0.58	27	6.4
8	36	69	55.5	207.8	28.7	2,245	8.80	0.79	33	6.9
9	63	50	31.8	157.4	23.8	1,640	5.09	0.63	33	5.8
10	80	90	51.4	239.1	33.9	2,365	8.22	0.57	25	6.0
11	22	55	40.6	200.2	25.0	2,065	6.50	0.74	37	4.8
12	18	42	30.0	179.6	14.7	1,795	4.80	0.71	43	3.3

Olmsted,[7] speaking of his experience with the use of fasting in the treatment of diabetes, says: "It was soon found that rather severe acidosis followed the period of complete starvation even in relatively mild cases. So impressed were we with the depression and weakness of patients during and following acidosis that some modification of the starvation routine was thought worth trying out." Some of our patients who had previously been subjected to fasting and were later made sugar free by our diet, volunteered the information that the earlier fasting method had left them in a state of exhaustion and extreme weakness and that they were astonished at their strength after they had become sugar free at our hands. The patient who was cited as Case 1, for example, said that after his previous fasting he had no desire to leave his bed; in contrast to this, on his thirteenth day in the hospital, when he became sugar free, he felt fresh after a two mile walk.

7. Olmsted, W. H.: M. Clinics N. America **4**:865 (Nov.) 1920.

Not only is fasting exhausting and unpleasant to the patient, but it may occasionally end in death. The dangers of complete fasting were pointed out in the Rockefeller Monograph [8] on the treatment of diabetes; Case 30 in that series is cited by the authors as "a typical example of acidosis with a fatal result on fasting," and "patient 35 developed malaise, nausea and drowsiness on fasting and the observers were convinced that unless fed he would have died in the typical intoxication." Joslin [9] has reported two patients who died with hypoglycemia as a result of fasting and Wilder [10] has observed that obese diabetics are especially susceptible to severe acidosis from fasting. We have had referred to us a patient who had been fasted for two weeks without becoming sugar free, and who had developed extreme weakness, nausea and vomiting; after four days in the hospital, during which she could retain no food, she died quietly without hyperpnea. She retained consciousness up to a minute or two before death. In this elderly

TABLE 11.—Efect of High Fat Diet on Lipoidemia

Case No.	First Percentage	Last Percentage	Interval, Days	Remarks
21-276	8.1	2.09	66	Case 4, this series
21-321	3.31	1.01	260	Case 1, this series
21-678	2.63	1.00	395	Case 3, this series; complicated by chronic pulmonary tuberculosis
21-1021	1.59	1.54	20	Case 5, this series
21-1392	2.73	1.10	38	Case 6, this series
21-3458	0.802	0.905	40	
21-3456	0.961	0.966	54	
21-3573	1.025	1.009	21	
22-2	1.33	1.15	19	
21-2418	0.869	0.948	14	Previously on diet for four months
22-36	0.930	0.933	17	
22-610	1.126	0.890	33	

patient whose symptoms had not been sufficiently severe during the three years that she had had diabetes to cause her to be treated, fasting ended in disaster. A summary of her record is appended (Case 9). More recently we have had the opportunity of observing a young diabetic in whom a fatal acidosis was precipitated by fasting; a summary of his record will be found as Case 10. The fact that fasting is always unpleasant, often dangerous and sometimes fatal, justifies one in rejecting it in favor of a procedure which avoids these difficulties and at the same time makes the patient sugar free.

Case 9 (20-709).—*History.*—An American housewife, aged 62 years, entered the hospital early in the evening of Nov. 9, 1920, in a state of extreme exhaustion. Little information could be obtained relative to her history. It

8. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in the Treatment of Diabetes, Monograph, Rockefeller Institute M. Research, No. 11, 1919.

9. Joslin, E. P.: M. Clinics N. America **4**:1723 (May) 1921.

10. Wilder, R. M.: M. Clinics N. America **5**:455 (Sept.) 1921.

was known, however, that she had had diabetes for three years, but that it had never disturbed her enough to cause her to commence systematic treatment. She was persuaded to begin treatment October 15; she was fasted for two days, then given green vegetables for three days, fasted three days more and finally given thrice cooked vegetables until November 5. During the last three days of this diet she became progressively more nauseated and vomited frequently. From November 5 until she entered the hospital she ate little and apparently retained nothing.

Examination.—At admission she was stuporous, but not unconscious, her speech was thick and she seemed loathe to exert herself sufficiently to talk. There was no hyperpnea, but her breath had an acetone odor. The knee jerks were diminished. Her urine contained albumin, sugar, diacetic acid and hyaline and granular casts. Her blood pressure was 165/70, the carbon dioxid tension of the alveolar air was 30 and blood sugar 0.33 per cent.

Comment.—During the time she was in the hospital, she retained no food and little of the water that was given her by mouth. Every few minutes, day and night, she vomited. Her temperature was always subnormal. On the night of November 12, she died quietly while the nurse was out of the room for two or three minutes.

Case 10 (21-3305).—*History.*—An American farmer, 26 years of age, entered the hospital Nov. 11, 1921, in deep coma. Little history could be obtained, but it was stated that diabetic symptoms were first noted less than five weeks before. Polyuria and polydipsia had been present only two weeks. Treatment was started two days before admission with the limitation of his diet to 2 quarts of milk on the first day and then complete starvation. On the morning of the second day of starvation he became stuporous and gradually passed into coma, coming to the hospital that evening.

Examination.—He was in deep coma with characteristic hyperpnea. His blood sugar was 1.07 per cent. and the carbon dioxid combining power of the blood plasma by the Van Slyke method was 18 volumes per cent. He died about five hours after admission to the hospital. Nothing important was found at necropsy.

We turn now to a consideration of the ability of patients to lead fairly active lives while they adhere to the maintenance diets prescribed for them when they leave the hospital. This diet is so constructed as to avoid the evils of undernutrition. The physiologic effects of undernutrition have been observed on a large scale during the recent war, and a review of these studies has been published by Graham Lusk.[11] These changes in metabolism result in a great mental and physical depression. The undernourished subject not only has not sufficient fuel for normal amounts of work, but lacks the desire to attempt work, mental or physical. Prolonged undernutrition results in chronic invalidism. The patient, if not actually confined to his bed or to a chair, is able to do little more than to get about the house unassisted. The woman who was mentioned above as Case 2 was bed-ridden on a diet allowing her 500 calories a day before she came to us. The condition of such a diabetic is pitiful; even the most moderate activity is denied him and he becomes a burden to his family and to himself

11. Lusk, G.: Physiological Effect of Undernutrition, Physiol. Rev. **1**:523, 1921.

and an economic loss to society. In contrast to this, our patients have returned to their original occupations, and have a bright, hopeful outlook on life. A few examples are cited.

CASE 11 (20-19).—*History.*—A railroad fireman, 22 years of age, entered the clinic Jan. 16, 1920, complaining of excessive thirst and polyuria. There was no history of diabetes in the family, and his past history was of no importance. The onset of the disease occurred abruptly during the early part of December, 1919, with polyuria, and increased thirst and appetite. By the first of January he was urinating every hour, and he went to a physician, who diagnosed diabetes. Between January 1 and his admission to the hospital his diet consisted entirely of milk. During the month that he had had diabetes his weight had fallen from 130 to 125 pounds.

Examination.—Nothing of interest was noted on physical examination. His urine was sugar free on the fourteenth day of a diet containing 16 gm. protein, 199 gm. fat, 10 gm. carbohydrate and 1,000 calories.

Comment.—January 21, he developed influenza, which was then epidemic; his diet was unchanged and he made an uneventful recovery. Feb. 20, 1920, he was discharged from the hospital on a diet containing protein, 25 gm.; fat, 175 gm.; carbohydrate, 15 gm.; 1,800 calories. This was gradually increased to contain protein, 55 gm.; fat, 220 gm.; carbohydrate, 35 gm.; calories, 2,400. Except for the first few weeks after discharge from the hospital he has been working hard and steadily, first in a machine shop and then on his father's farm. On a few occasions he has fired a locomotive and states that he noticed no unusual fatigue. At present, two and a half years after admission, he is working on the farm, says that he feels entirely well and is sugar free on the diet.

CASE 12 (20-346).—*History.*—A housewife, 32 years of age, was admitted to the hospital April 19, 1920, complaining of weakness and polyuria. There was no history of diabetes in the family. During her past life she had had many attacks of bronchitis, and she had had one attack of tonsillitis several years before admission. In January, 1919, she had influenza and did not regain her strength after it as she thought she should. She also suffered from polyuria and swelling of the feet. A physician told her that she had diabetes and forbade the use of foods rich in carbohydrate. Her urine had never been sugar free from this time until she came to the hospital, and weakness was progressive. At the time when we first saw her, this latter was her most serious complaint. She stated that she was entirely unable to attend to her household duties or to care for her 6 year old child, and that if she was out of bed for any length of time she fainted and had to be carried back.

Examination.—Nothing of importance was noted in the physical examination.

Comment.—On a diet containing 16 gm. protein, 95 gm. fat, 8 gm. carbohydrate and 950 calories her urine became free from sugar on the fourth day and the ferric chlorid reaction was negative on the eighth day. Her diet was increased to contain 55 gm. protein, 220 gm. fat, 35 gm. carbohydrate and 2,400 calories. She has kept in constant touch with us, and with the exception of a short period when she had a severe acute bronchitis, she has always been sugar free, a period of twenty-six months. She is doing her housework, and feels as strong as she did before the onset of her diabetes.

CASE 13 (19-286).—*History.*—A Jewish salesman, 40 years of age entered the hospital June 5, 1919, with a diabetes that had developed abruptly ten years before. There was no family history of diabetes, and his previous history was of no importance. At the time of onset of the usual diabetic symptoms, his weight had been 172 pounds; his weight at admission was 136 pounds. His vision had failed rapidly, and when first seen by us his left

eye was almost blind. There had been increasing numbness and tingling of the feet and legs for the past few months, and he was unable to work because of weakness.

Physical Examination.—This showed nothing of importance, except evidence of peripheral and aortic arteriosclerosis. His blood sugar was 0.40 per cent., his urine contained sugar and diacetic acid and his hemoglobin was 110 per cent. with 6, 320,000 red blood cells.

Comment.—On a diet containing protein, 15 gm.; fat, 90 gm.; carbohydrate, 10 gm.; 900 calories, he became sugar free in one day. His diet was increased by steps until he was receiving protein, 48 gm.; fat, 243 gm.; carbohydrate, 15 gm.; calories, 2,440. The patient returned to the hospital March 31, 1920, for examination. His urine was free from sugar and his blood sugar was 0.13 per cent. He had adhered to the diet previously prescribed and was discharged with the same diet. At a third admission, Feb. 1, 1921, he was still sugar free, with a blood sugar of 0.12 per cent. and no diabetic symptoms. He was discharged on a diet which allowed him protein, 55 gm.; fat, 220 gm.; carbohydrate, 35 gm.; calories, 2,440. In December, 1921, he reported that he is still sugar free and feeling entirely well. During these three years he has been active as a traveling salesman, and has in no way been disturbed by his diabetes. His weight is 120 pounds.

Case 14 (18-519).—*History.*—An American farmer, 57 years old, entered the hospital Oct. 10, 1918, complaining of weakness and ulcer on his foot. He had always been healthy until eight years before when he began passing large quantities of urine. Aside from the omission of bread from his diet, there had been no treatment of the diabetes. On two previous occasions he had ulcers on his feet that were slow in healing. The one that brought him to the hospital appeared about five weeks before. Eight years before he weighed 187 pounds and his admission weight was 129 pounds.

Examination.—Arteriosclerosis was marked, his urine contained diacetic acid and 63 gm. glucose in the first twenty-four hour specimen, and his blood sugar was 0.59 per cent.

Comment.—October 24, his urine was free from sugar and his diet was increased by steps until it contained 3,050 calories, from 60 gm. protein, fat, 300 gm., and carbohydrate, 25 gm. He was left on this diet until Oct. 21, 1921, when it was changed to contain protein, 55 gm.; fat, 220 gm.; carbohydrate, 35 gm., and 2,340 calories. The patient's wife, who has been caring for his diet, says that he has adhered to it religiously, and that during the whole time he has been able to do his work on the farm.

6. *Prognosis.*—The question naturally arises as to whether or not all these advantages accrue to the diabetic at the expense of duration of life. That is, will the use of a diet such as we have advocated cause in itself a downward progress of the disease with a loss of tolerance and an earlier death than might be expected under the other methods of treatment. While our experience with high fat diets is still brief in proportion to the chronicity of the disease and we must therefore be somewhat cautious in our conclusions in this regard, we have as yet seen no reason for believing that such is the case. We have a certain amount of information that seems to bear on the question and which apparently indicates that the prognosis in patients on the high fat, low protein diets is at least as good as that in patients on other diets.

Such evidence may be obtained in both of two ways; first, by recording any change in tolerance that may occur in individual cases

from time to time during the prolonged use of the diet; second, by a statistical comparison of the outcome in our patients with that of patients on other diets.

Carbohydrate Tolerance.—While we have not as yet observed a sufficient number of patients over a sufficient length of time to make us willing to affirm that this treatment is never attended by downward progress, we have been able to follow some severe cases of diabetes long enough to show that a diet containing roughly the normal caloric requirement is at least not inevitably attended by loss of tolerance within the period of observation. The records of several such patients have been presented in summary in this paper.

In our whole series we have seen no evidence of loss of tolerance in a patient who has adhered to the diet and, therefore, we have no reason for believing that downward progress is an accompaniment of a maintenance diet. We had one patient under observation in whom diabetes was complicated by a wide spread pulmonary tuberculosis whose capacity for the utilization of carbohydrate steadily declined until he died of the tuberculosis fourteen months after the initiation of treatment. A similar loss of tolerance from a pyogenic infection was observed in Case 15. The disastrous effect of infections on the glucose tolerance of diabetics is well known, and in these cases explains the observed downward progress.

Case 15 (21-3332).—*History.*—A boy, aged 7, came for treatment Nov. 14, 1921, with diabetes that had developed in connection with a suppurative mastoiditis in May, 1920. He had had careful dietetic treatment during the interval and for several months previous his diet had contained protein, 60 gm.; fat, 60 gm., and carbohydrate, 10 gm., on which he had had glycosuria most of the time. He was desugarized by a diet containing protein, 25 gm.; fat, 100 gm., and carbohydrate, 12 gm. His diet was increased to protein, 30 gm.; fat, 130 gm.; carbohydrate, 18 gm.

During January, 1922, he developed an acute upper respiratory infection and eventually a pansinusitis. Glycosuria returned in a progressively increasing degree and he died May 20, 1922.

Duration of Life.—Conclusions regarding the duration of life in relation to any treatment used in the management of a chronic disease are difficult to draw because of the many more or less unavoidable sources of error that enter into a biologic problem of this sort. Statistical compilations of the average duration of life in years of diabetics undergoing different forms of treatment might at first thought seem to answer the question mathematically and beyond doubt. But statistics to be of value must deal with only one variabie or else all other variables must be thoroughly understood and be under control. Such is not the case in the present problem. Some of the improperly controlled variables which inevitably occur in series of cases extending over long periods of time are the following:

1. The term diabetes mellitus is applied to several types of persistent glycosuria which vary greatly in severity and prognosis regardless of treatment. Wilder [10] recently made another effort to classify diabetics, and divided them into five groups whose clinical manifestations and progress are so different as to make them seem like different diseases. Unless series that are being compared contain equal percentages of the different kinds of diabetics, deductions from the statistics will be erroneous in just so far as the types represented are numerically unequal.

2. It is probably true that all diabetics are guilty at one time or another of small indiscretions in diet, and many of larger ones. The effect of such indiscretions on duration of life is not known and therefore becomes a variable whose magnitude is undetermined. Experience seems to show that the effect of indiscretion varies enormously from patient to patient. For example, the patient reported as Case 16 died apparently as the result of a single indiscretion, while the patient reported as Case 17 appears to have recovered from her diabetes while living on an unrestricted diet.

CASE 16 (19-170).—*History.*—A woman, 38 years of age, entered the hospital April 3, 1919, because of sexual anesthesia and diabetes. She stated that her nine children had diabetes, but this could not be verified. Her diabetic history was not clear cut, consisting of pruritis vulvae at intervals since the age of 14, nocturia as long as she can remember, tingling of her legs for fifteen years, boils nine years before and glycosuria first discovered in 1910. Her weight at the age of 21 was 135 pounds, and at admission to the hospital was 131 pounds.

Examination.—Her blood sugar at admission was 0.57 per cent. and her urine contained 74 gm. glucose in the twenty-four hour specimen.

Comment.—On a diet containing 16 gm. protein, 90 gm. fat and 10 gm. carbohydrate her urine became sugar free on April 17, and her blood sugar was 0.19 per cent. At this time her husband brought her some food beyond what had been prescribed, glycosuria returned, her blood sugar rose to 0.32 per cent., vomiting developed, and her general condition became progressively worse. Actual coma did not appear until May 3 after three days of fasting and she died the next day.

Pathologic Diagnosis from Necropsy.—Diabetic coma; subacute parenchymatous nephritis; acute toxic hepatitis; thyroid adenoma; atrophy and fibrosis of pancreas.

CASE 17 (19-38).—*History.*—A girl, aged 18, was transferred to our clinic from the department of genito-urinary surgery, Jan. 22, 1919. She had come to the hospital for treatment of gonorrhea, and glycosuria had been discovered during the routine urine examination. There had been no diabetic symptoms. Her father and mother had died during her childhood and no family history could be obtained.

Examination.—Her general examination showed nothing of importance. The urine contained 184 gm. glucose in the first twenty-four hours, but she insisted on leaving the hospital.

Comment.—A letter from her home physician states that her urine is sugar free and that she is feeling entirely well without dieting.

3. The prognosis in diabetes is very closely related to the complications of the disease. Diabetics treated in institutions of different types show variations in percentages of individual complications. The clinic situated in a region to which many patients come from long distances for the treatment of tuberculosis sees more diabetic patients with tuberculosis than does the average clinic. In a hospital known chiefly for its surgery, the internist cares for a large percentage of diabetics with surgical diseases. The diabetic specialist in a large general hospital must add to his group many patients entering because of serious infections and major surgical conditions, to whom the diabetes is unknown or of minor importance, whereas the physician confining himself to the treatment of private diabetic patients is less likely to have to care for these milder cases of diabetes in which life is ended by the major diseases which brought the patients to the hospital. The statistical outcome of a group is importantly affected by the number of patients who enter the hospital in coma, but this number will vary with the location of the hospital. The general hospital in the big city will receive more such cases than an institution such as the university hospital located as it is in the small town, since patients in coma are not transported a long distance to a hospital.

4. Diabetics are subject to the prevalent small infections. The lasting effect of these small infections cannot be guessed at. Furthermore, statistics concerning any group of diabetics may be seriously affected by an epidemic in their community; for example, three of the seventy-three patients originally reported on by us died of influenza. While influenza was pandemic in this country at the time, it illustrates the fact that such a disease may influence the statistics either because of its effect on a small series of cases, or because it might be local.

5. It is obvious that statistics dealing with the duration of life from the onset of the diabetes are greatly influenced by the efficacy of the treatment before the patient came to the physician compiling the statistics. The previous treatment may effect the total duration of the disease in either of two ways; either the proper management of the patient may have given him a long life before he came to the physician reporting the statistics, or improper treatment may have aggravated the disease or allowed complications to develop that injure the prognosis. For example, the appearance of our statistics on young diabetics is improved by the addition of Case 1, the patient having been kept alive for seven years by previous treatment, while the patient described as Case 18 (cited below) was mildly diabetic, and came to us with an overwhelming and fatal infection which had been allowed to develop because her diabetes was uncontrolled.

CASE 18 (21-1507).—*History.*—A housewife, 57 years of age, entered the hospital June 2, 1921, with a massive infection in her feet and legs, complaining of the usual symptoms of diabetes. Six years before she was troubled by pruritis vulvae, and during the following year polyuria and polyphagia developed. At this time a physician diagnosed the diabetes. For eight weeks she was on a diet of green vegetables and bran, but since that time there had been no dietetic treatment. Her weight fell from 200 pounds to 140 pounds. Her vision had been failing for a year and constipation had been obstinate. About four years ago she began having blisters on her feet, which would rupture, heal very slowly and then appear again. Several weeks ago her feet became swollen, red, and so painful that she could not walk on them.

Examination.—On examination it was noted that there was marked sclerosis of the peripheral vessels and evidence of aortic sclerosis. The knee jerks four years ago she began having blisters on her feet, which would rupture, heal very slowly and then appear again. Several weeks ago her feet became swollen, red, and so painful that she could not walk on them.

Comment.—Throughout her stay in the ward she had an irregular fever and a leukocytosis of from 22,300 to 35,300. Her hemoglobin was 60 per cent. and she had 3,050,000 red cells. Her blood sugar was 0.21 per cent. and her urine contained sugar but no diacetic acid. In spite of free drainage of her feet, chills and fever continued, she became weaker, the pulse feebler, respirations slower and she died during the night of June 12.

6. Accurate knowledge of the length of life after the onset of diabetes is often unobtainable because of the impossibility of determining the date of onset. The discovery of glycosuria by the insurance examiner or during the routine urinalysis in a hospital gives one no information about the duration of the disease up to that time. Some patients cannot remember when the symptoms began, others mention symptoms many years before which may or may not have been diabetic, and in others the onset was so insidious that the physician cannot determine the date of onset.

7. The statistical outcome of the treatment of a group of patients must be influenced by the type of subjects with whom one has to deal. The prognosis is influenced by the patient's intelligence and his social status. It is probable that the improvement during the last decade in the treatment of diabetes has been due very largely to the realization of the importance of instructing the patient in his own care. This instruction can be carried only as far as the patient has ability to learn. It follows then that the prognosis in a given case is largely dependent on the subject's mental capacity. One of our patients is suffering from Korsakoff's psychosis and entirely unable to care for herself; another, with a condition diagnosed constitutional psychopathic state by the department of psychiatry, whose family is trying to keep him to the diet, is reported to be stealing food from the garbage cans of the neighborhood. The deaths of such patients from diabetes or any other cause bear no relation to attempts at treatment.

The social status of the patient influences the prognosis because of two factors. Persons compelled to obtain their food at public eating

houses find it impossible to adhere rigidly to the diet because of inability to obtain proper foods or to have them measured. One of our patients, a farm hand, is very much discouraged because he has not been able to find work on a farm where his diabetic meals will be prepared for him. Others, under economic pressure, are unable to increase their expenses by the small amount necessary to supply the diet. One of them is living on thirty cents a day, and eats little but rolls and coffee.

8. An important variable in the statistical study of diabetics is the physician himself. Success in the treatment depends, in part, on the ability of the physician in impressing on the patient the importance of adhering to the diet, and, in part, on the amount of instruction that can be given the patient in the management of his food. In the comparison of statistics from different institutions these elements cannot be ignored.

9. An important factor in the success of treatment of diabetes is the home physician. The adherence of the patient to a diet depends, in part, on the belief of the home physician in the importance of strict adherence. The damaging effect to statistics of lack of cooperation between the specialist and the general practitioner is shown in the following example (No. 19).

CASE 19 (20-475).—*History.*—An American woman, aged 33 years, entered the hospital July 12, 1920, complaining of weakness and loss of weight. There was no family history of diabetes. Her diabetes developed abruptly in July, 1919, with polyphagia, polydipsia, polyuria, weakness, and loss of weight. For the past six months she had noticed progressively increasing numbness of her arms and legs. Her weight at the onset of the disease was 109 pounds and her weight at admission was 61 pounds.

Examination.—Except for loss of the knee and Achilles reflexes, her physical examination was negative. Her blood sugar was 0.42 per cent., and her urine gave a strong reaction to ferric chlorid.

Comment.—On the tenth day of a diet containing 15 gm. protein, 90 gm. fat, and 12 gm. carbohydrate, her urine gave a negative reaction to ferric chlorid and was sugar free. She was discharged from the hospital August 28 without glycosuria or evidence of acidosis on a diet which allowed her 28 gm. protein, 140 gm. fat and 20 gm. carbohydrate. A letter from her sister stated that she adhered to the diet until late in October when the family physician advised her to let the patient have anything she wanted. She died Nov. 18, 1920.

We have cited a number of important reasons for using great caution in applying statistics to the study of the comparative effects of different treatments on the course of the disease in the diabetic patient, but in spite of these objections there is undoubtedly something to be learned from the tabulation of the available data concerning the status of our 190 patients. This information is contained in Table 12.

It will be noted that of these 190 patients, treated between March 1, 1918, and July 1, 1922—a period of four and one third years—forty-five (23.7 per cent.) are dead, fourteen (7.4 per cent.) are not traced and 132 (68.9 per cent.) are alive. If the fifteen patients who died in

TABLE 12.—PRESENT STATUS, BY DECADE OF ONSET AND YEAR OF FIRST TREATMENT, OF ALL PATIENTS TREATED SINCE INCEPTION OF HIGH FAT DIET

	Age of Onset								
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total
Total Cases:									
1918	0	0	5	4	2	5	1	0	17
1919	1	4	3	6	10	10	3	1	38
1920	1	0	6	5	7	13	2	0	34
1921	3	7	8	10	7	18	11	1	65
1922	1	3	2	8	11	10	0	1	36
Total	6	14	24	33	37	56	17	3	190
Died in Hospital:									
1918	..	..	2	..	..	..	..	..	2
1919	..	1	..	1	..	1	..	..	3
1920	..	..	..	1	2	1	1	..	5
1921	..	..	1	..	..	1	..	..	2
1922	..	..	1	..	1	1	..	..	3
Total	0	1	4	2	3	4	1	0	15
Dead—Discharged Untreated:									
1918	..	..	..	1	..	..	..	..	1
1919	..	..	..	..	1	1	..	..	2
1920	..	..	2	..	..	..	..	..	2
1921	..	1	..	..	..	.	..	..	1
1922	..	..	..	..	..	..	..	..	0
Total	0	1	2	1	1	1	0	0	6
Died—Treated:									
1918	..	..	1	..	..	2	..	..	3
1919	..	2	..	..	..	1	..	..	3
1920	..	..	2	2	3	3	1	..	11
1921	1	..	2	..	..	1	1	1	6
1922	..	..	..	..	..	1	..	..	1
Total	1	2	5	2	3	8	2	1	24
Untraced:									
1918	..	..	..	1	..	1	1	..	3
1919	..	..	2	3	1	1	1	..	8
1920	..	..	..	1	..	1	..	..	2
1921	..	..	..	..	..	..	1	..	1
1922	..	..	..	..	..	..	..	..	0
Total	0	0	2	5	1	3	3	0	14
Alive:									
1918	..	..	2	2	2	2	..	..	8
1919	1	1	1	2	7	5	2	1	20
1920	1	..	2	1	3	9	..	..	16
1921	2	6	5	10	7	16	9	..	55
1922	1	3	1	8	10	8	..	1	32
Total	5	10	11	23	29	40	11	2	131
Summary:									
Total cases									190
Total dead									45
Total missing									14
Total alive									131

the hospital, the eight who were discharged against advice with glycosuria and the fourteen who are untraced be subtracted from the total of 190, there remain 153 who were discharged sugar free. These 153 patients are the only ones who give us evidence concerning the effect of

the diet when used over a long period of time. Of these 153 patients, twenty-four (15.7 per cent.) are dead and 129 (84.3 per cent.) are living. Obviously, there is no way of knowing how many of these patients adhered rigidly to the prescribed diets.

The forty-five dead patients fall into three groups: viz., fifteen who died in the hospital, six who were discharged against advice with glycosuria and twenty-four who died after having been discharged from the hospital sugar free. The first group is presented in Table 13. It will be seen that five of these died in coma; of these four entered in coma and were not treated by the method under discussion; the fifth went into coma after breaking diet. The patient who died

TABLE 13.—PATIENTS DYING IN HOSPITAL

Number	Date of Admission	Date of Death	Condition at Admission	Cause of Death	Age at Onset	Age at Death	Remarks
18-639*	11/11/18	11/12/18	Coma	Coma	..	29	No history
18-679	12/ 8/18	9/30/20	.....	Chronic pulmonary tuberculosis	26	28	No glycosuria, no acidosis at death
19-170	4/ 3/19	5/ 4/19	.....	Known to have broken diet; coma	7	38	
19-641	1/29/20	1/30/20	Influenza	Pneumonia	33	36	
19-650	12/26/19	12/29/19	Coma	Coma	57	60	
20-423	6/ 7/20	7/13/20	Hematuria	Bronchopneumonia	61	63	No glycosuria nor acidosis at death
20-443	6/16/20	6/28/20	Advanced tuberculosis	Pulmonary tuberculosis	45	46	No glycosuria nor acidosis at death
20-481	7/14/20	7/15/20	Suppurative mastoid; coma	Septicemia	35	47	
20-709*	11/12/20	11/12/20	Exhaustion vomiting	Inanition	59	62	Previous fasting
20-753	12/ 3/20	12/17/20	Ventral hernia	Postoperative pneumonia	46	48	Died in surgical ward; necropsy; mild diabetes
21-1507*	6/ 2/21	6/13/21	Osteomyelitis of foot	Septicemia	53	59	
21-3305	11/11/21	11/11/21	Coma	Coma	26	26	
22-27	1/10/22	2/ 2/22	Pyelonephritis; pyemia	Septicemia	49	50	No glycosuria nor acidosis at death
22-309	2/13/22	2/15/22	Coma	Coma	24	27	
22-477	3/16/22	4/15/22	Gangrene legs	Gas gangrene	53	56	Necropsy

* Summary of record elsewhere in paper.

of inanition as the result of previous fasting has been described as Case 9. All but two of the remaining cases died of infection acquired before entering the clinic. One patient (20-753), mildly diabetic, died of pneumonia following an operation for repair of a ventral hernia at a time when she was sugar and ketone body free. The remaining patient (20-423) died of bronchopneumonia following cystoscopy, without glycosuria or evidence of acidosis. None of these deaths are of significance in estimating the value of the high fat diet.

The status of the patients who left the hospital against advice is presented in Table 14. Seventy-five per cent. of the patients who refused dietary treatment are dead. This emphasizes again the importance of keeping the diabetic sugar-free regardless of the method employed.

The twenty-four patients who died after leaving the hospital on the diet are presented in Table 15. Four patients are known to have died in coma and all of them are known to have discarded the diet.

TABLE 14.—Status of Patients Leaving Hospital Against Advice with Glycosuria

Case No.	Date of Admission	Date of Discharge	Date of Onset	Date of Death	Age at Onset	Age at Admission	Age at Death	Duration After Discharge	Cause of Death or Condition if Alive
18-263	5/27/18	6/ 4/18	Jan., 1918	7/1/18	35	38	38	1 month	?
18-468	9/12/18	9/16/18	Jan., 1918	.....	29	39	..	.....	Refused treatment; glycosuria
19-38	1/22/19	2/14/19	?	.....	?	18	..	.....	Unrestricted diet; no glycosuria
19-411	8/26/19	9/ 3/19	1917	12/14/20	51	53	54	1.2 years	"Chronic diarrhea"
19-201	4/17/19	4/26/19	1914	July, 1921	47	52	54	2.2 years	Gangrene both legs
20-516	8/ 5/20	8/12/20	1915	8/20/20	30	35	35	1 week	Coma
20-676	10/21/20	10/27/20	March, 1920	9/29/21	26	26	27	1.2 years	Coma
21-3115	10/31/21	11/ 1/21	June, 1921	Jan., 1921	15	15	16	8 months	Pneumonia

TABLE 15.—Cases Discharged Without Glycosuria

No.	Date of Admission	Date of Death	Age at Onset	Age at Death	Cause of Death	Total Duration, Years	Duration After Start of Treatment	Remarks
18-168	4/10/18	10/ 1/21	57	66	Diabetic gangrene	8.5	3½ yrs.	Chronic nephritis with hypertension
18-298	6/12/18	Spring, 1921	53	59	Apoplexy	6.0	2 yrs.	
18-382	7/25/18	Jan., 1919	27	31	Influenza	4.0	6 mos.	
19-218	4/28/19	1/ 7/20	56	60	Uremia	11.0	14 mos.	Mild diabetes; severe nephritis
19-229	5/ 1/19	5/ 9/19	50	55	Carcinoma of uterus	5.0	1 yr.	
19-263	5/22/19	11/23/19	61	67	?	6.0	6 mos.	
19-306	6/20/19	1/21/22	64	70	Gangrene	6.0	2.6 yrs.	
19-444	9/ 5/19	2/ 8/19	16	18	Influenza	2.0	6 mos.	
19-537	10/22/19	July, 1920	20	21	Coma	1.5	9 mos.	Motor trip; ate everything; died short time after arriving
20-24	1/20/20	Aug., 1920	26	27	?	1.6	8 mos.	
20-211	2/19/20	4/18/21	50	59	Apoplexy; Bright's disease	8.8	14 mos.	Mild diabetes; severe nephritis
20-294	3/23/20	5/24/20	27	28	Convulsions	0.8	2 mos.	Cerebrospinal syphilis
20-426	6/ 8/20	Sept., 1920	33	34	Coma ?	1.4	3 mos	
20-427	6/ 9/20	May, 1922	44	47	?	3.2	23 mos.	
20-475	7/12/20	11/18/20	32	33	Coma	1.2	4 mos.	Home physician told her to eat what she wanted; died two weeks later
20-486	7/16/20	2/ 1/22	62	68	Cardiac failure	5.7	1.5 yrs.	Chronic myocarditis
20-632	10/ 1/20	7/ 5/21	59	65	Carcinoma of breast	6.0	8 mos.	
21-19	1/10/21	2/15/21	71	76	Apoplexy	5.2	1 mo.	Mild diabetes; severe nephritis
21-276	2/ 7/21	Jan., 1922	21	22	Coma	1.3	11 mos.	Tried "patent medicine"; died in three weeks
21-2329	8/17/21	1/22/22	54	64	Chronic pulmonary tuberculosis	10.3	5 mos.	Advanced tuberculosis at admission
21-2708	9/20/21	3/ 5/22	52	53	Coma	1.3	5 mos.	Left against advice
21-2954	10/12/21	Feb., 1922	61	68	Angina pectoris	7.4	4 mos.	
21-3332	11/14/21	5/12/22	6	8	Maxillary sinusitis	2.0	6 mos.	
22-1246	5/ 3/22	6/ 2/22	55	55	?	0.3	1 mo.	Discharged against advice; sugar-free

A fifth is believed to have died in coma, though little is known about her death. That is, of 167 patients discharged sugar free, only five have died in coma, and four of these are known to have discarded their diet. These statistics demonstrate clearly the innocuousness of the

high fat diet in relation to the induction of acidosis. Two died of gangrene. The rest died of causes not primarily diabetic.

A summary of the causes of death of all these forty-five patients, including those who died in and out of the hospital, is found in Table 16. Joslin [12] has pointed out that coma as a cause of death has decreased from 68 per cent. of his fatal cases treated before 1914 to 55 per cent. since he has employed fasting and severe undernutrition. This he cites as evidence of improvement in treatment. It is, therefore, interesting to note that in our relatively small series of fatal cases, only 27 per cent. have died in coma.

TABLE 16.—CAUSES OF DEATH IN ALL KNOWN TO HAVE DIED SINCE THE INCEPTION OF HIGH FAT DIET

	Number	Per Cent.		Number	Per Cent.
Coma	12	26.7	Uremia	1	2.2
Gangrene	4	8.6	Central nervous system syphilis	1	2.2
Pneumonia	6	13.3	"Chronic diarrhea"	1	2.2
Tuberculosis	3	6.7	Carcinoma	2	4.4
Septicemia	3	6.7	Apoplexy	3	6.7
Inanition	1	2.2	Suppurative sinusitis	1	2.2
Angina pectoris	1	2.2	Unknown	5	11.1
Cardiac failure	1	2.2			

TABLE 17.—STATUS OF ALL PATIENTS AFTER MORE THAN FOUR YEARS USE OF TREATMENT

	Williams		Authors' Series	
	Number	Per Cent.	Number	Per Cent.
Total	304	100	176*	100
Living	201	66	131	75
Dead	103	34	45	25

* Excluding 14 cases lost.

While we have pointed out the pitfalls encountered in the use of comparative statistics, it may, nevertheless, be of some value to tabulate our results beside those of competent observers using other methods. It is, of course, not necessary to compare this group with one treated previous to 1914 because of the great improvement in the treatment of diabetes mellitus that followed this date. Comparison, however, with such statistics as those of Williams [13] dealing with 304 cases treated during the five year period 1915-1920 may be profitable (Table 17).

Allen [14] has recently published the end results in patients treated in the Physiatric Institute during 1919, 1920 and 1921. Since the

12. Joslin, E. P.: Today's Problem in Diabetes Mellitus in Light of 930 Fatal Cases, J. A. M. A. **78**:1506 (May 20) 1922.

13. Williams, J. R.: Evaluation of the Allen Method of Treatment of Diabetes Mellitus, Am. J. M. Sc. **162**:62, 1921.

14. Allen, F. M., and Sherrill, J. W.: Clinical Observations on Treatment and Progress in Diabetes, J. Metabolic Research **1**:391, 1922.

number of patients lost from observation is not tabulated, a strict comparison may not be warranted. In Table 18 the percentage of deaths of the two groups treated is presented; all deaths are included for each observer, regardless of the condition of the patients at admission or their adherence to treatment.

Allen has further tabulated his mortality by excluding those patients who came to him with gangrene, tuberculosis, serious acidosis and neoplasms and subsequently died of such complications. In Table 19 we have compared our mortality with Allen's on this same basis.

A third comparison may be made with the mortality statistics recently published by Joslin [12] of the group treated by him, in hospitals, during the period between April 1, 1919, and December 31, 1922. In Table 20 will be found his data and those of the corresponding group of our series. It will be noted that 8 per cent. of our patients

TABLE 18.—Comparison of Allen's and Authors' Statistics for 1919, 1920 and 1921 as of Jan. 1, 1922

	Total	Dead	Mortality, Per Cent.
Allen	504	86	17.1
Authors' series	137	26	18.8

TABLE 19.—Similar Comparison with Deaths of Patients Entering with Gangrene, Tuberculosis, Serious Acidosis and Neoplasm Omitted

	Total	Dead	Mortality, Per Cent.
Allen	480	62	12.0
Authors' series	128	17	13.3

died in the hospital, whereas only 2 per cent. of Joslin's died in the hospitals. Since our greater initial mortality is not related to the dietetic plan, it does indicate that we receive a considerably larger proportion of patients who are suffering, when first seen, from serious illnesses which will shortly end their lives, regardless of their diabetic state. In spite of this our mortality is slightly less than his. It is also worthy of note that the average duration of life of those dying in his series was 4.5 years, and in ours, 4.8 years.

It is apparent that, in so far as our statistics go and in so far as deductions from them are justifiable, there is no shortening of the duration of life of the diabetic by the use of a low protein, low carbohydrate, high fat, maintenance regimen. The advantage to the diabetic patient of a diet deriving most of its energy from fat, which, while still controlling the diabetic state, allows him a wide range of activities and avoids the chronic invalidism of severe undernutrition, is apparent. This is admitted by the most ardent adherents of the

undernutrition regimen, provided it can be demonstrated to them that such a diet does not increase the danger of coma nor shorten the duration of life. We have shown that these two fears are groundless. None of our patients has gone into coma as the result of the initiation of this treatment and only half as large a percentage of our fatal cases have resulted in death in coma as in Joslin's series. Our mortality statistics are not importantly different from those of the observers who use severe undernutrition. The improvement in the treatment of diabetes since the introduction of undernutrition in 1914 is undoubted. The high fat maintenance regimen has been shown to permit the diabetic the same expectancy of life as undernutrition. Since the high fat regime carries the out-standing benefit of undernutrition, namely, an increased duration of life, and at the same time avoids the incapacity that inevitably results from prolonged undernutrition, it must necessarily follow that undernutrition should be supplanted by this dietetic method.

TABLE 20.—Diabetic Patients Treated from April 1, 1919, to Dec. 31, 1922, on Jan. 1, 1922

	Authors		Joslin [12]	
	Number	Per Cent.	Number	Per Cent.
Cases, total	124	100	536	100
Cases, traced	117	94	508	95
Deaths in hospital	10	8	11	2
Deaths in and outside hospital	26	21	118	23

7. Minor Considerations.—Besides these six major considerations which must enter into a discussion of the treatment of diabetes, there are a few matters of less importance which, nevertheless, should not be ignored in judging of the value of any dietetic regimen. Chief among these are palatability of the diet, its safety in relation to surgical operations and its effect on the gastro-intestinal tract.

On first thought it would seem that it must be difficult to provide diets containing so much fat and so little carbohydrate that are still palatable. To the skilled dietitian this is not a serious problem. Not only can the meals be made attractive, but sufficient variety can be offered so that there is no monotony and the patient need not be surfeited with any one kind of food.[15]

The surgeon will ask whether such a diet as has been described may properly be used as a preparation for operation. We have had a not inconsiderable experience in this matter, and we have not varied from our routine in preparing our patients for operations. Such minor operative procedures as tooth extractions, tonsillectomies, and

15. Stewart, D.: Feeding High Fat Diets in Diabetes, Mod. Hosp. **18**:164, 1922.

extraction of cataract have been frequent. Several have had amputations of fingers or toes, removal of osteomyelitic bones, and uterine curettages. We have had to deal with the usual number of diabetics who required major surgical operations. None of these patients has developed a serious acidosis. One patient died of postoperative pneumonia which complicated the repair of a ventral hernia without the reappearance of glycosuria; at necropsy a wide spread pneumonia of the influenzal type was found. The remainder of the patients made an uneventful convalescence.

It might be questioned whether a diet so rich in fat may not be accompanied by diarrhea. Such has not been our experience; in no one of our 190 cases has our diet been responsible for a diarrhea.

SUMMARY OF RESULTS

A low protein, low carbohydrate, high fat diet fed a large group of diabetic patients since March 1, 1918, (1) produced and maintained an aglycosuric state; (2) was not attended by acidosis and caused its disappearance when present (short of coma) at the beginning of treatment; (3) maintained nitrogen balance; (4) did not cause a hyperlipoidemia and was attended by its disappearance in those patients in whom it was present at entrance; (5) supplied sufficient energy to (*a*) avoid the evils of fasting and undernutrition and (*b*) permit an amount of activity compatible with earning a livelihood; (6) was, within the limits of our observations, not attended by downward progress in uncomplicated cases.

DISCUSSION

In the construction of the diet that we have recommended we had in mind as the first requirement that its glucose equivalent be low in relation to the total calories. Since all of the carbohydrate, 58 per cent. of the protein, and, perhaps, 10 per cent. of the fat, are converted during metabolism into glucose, it is apparent that such a diet must be composed chiefly of fat. If the glucose equivalent of different types of diabetic diets are calculated by means of these figures, as suggested by Woodyatt [16] the interesting results shown in Table 21 are obtained.

It is apparent that the high fat diet throws into the metabolism much less glucose in proportion to its caloric content than do the other two types of diet.

Relation of High Fat Diets to Acidosis.—Owing to the lowered capacity of the diabetic to burn glucose, there is a proportional decrease in his ability to burn fat. Some glucose must be oxidized to assure the complete oxidation of fat. The maximum fat-carbohydrate ratio

that is safe has not been established beyond question. On the basis of the available data, Woodyatt[16] has suggested that if the ratio $\frac{\text{Fatty Acid}}{\text{Glucose}}$ [17] is greater than 1.5, acidosis will develop. Our standard diets far exceed this ratio. For example, a standard maintenance diet, composed of protein, 55 gm., fat, 220 gm., carbohydrate, 35 gm., gives a ratio of 2.5. In spite of these high fat values none of the patients developed an acidosis. Of still more importance is the fact that in those patients who came in with an acidosis short of coma, this acidosis has disappeared on the diet. Furthermore, we have even exceeded such high fat: carbohydrate ratios in individual cases without the induction of acidosis. A striking example of this was presented as Case 2. Reference to Table 3 will show that this young diabetic, who entered the hospital with a marked acidosis as shown by his clinical condition, the carbon dioxid combining power of his blood plasma and the ferric chlorid reaction of his urine, showed a prompt

TABLE 21.—Glucose Equivalents of Different Diets

Protein	Fat	Carbohydrate	Calories	Glucose Equivalent
180	138	10	2,000	128.4
90	113	130	2,000	191.6
50	187	30	2,000	78.1

disappearance of the symptoms and signs of the acidosis on our routine desugarization diet. Later he tolerated without acidosis a maintenance diet whose $\frac{\text{Fatty Acid}}{\text{Glucose}}$ was 4.1. Our experience with this group of diabetics has convinced us that much higher fat: carbohydrate ratios than those allowed by the calculation of Woodyatt may safely be employed.

Ladd and Palmer[18] have also studied the question of the carbohydrate-fat ratios in relation to ketonuria. Diabetic patients were freed from sugar, their sugar tolerance determined and they were then placed on diets which contained enough protein to maintain nitrogen equilibrium with the fat and carbohydrate given. During different periods the protein was kept constant and the amount of carbohydrate was reduced in proportion to the fat until ketone bodies showed a definite increase in the urine. Table 22 shows the percentage relationship of fat and carbohydrate and the total available carbohydrate

16. Woodyatt, R. I.: Objects and Method of Diet Adjustment in Diabetes Mellitus, Arch. Int. Med. **28**:125 (July) 1921.

17. Fatty acid = 0.9 fat plus 0.46 protein; glucose = carbohydrate plus 0.58 protein plus 0.1 fat.

18. Ladd, W. S., and Palmer, W. W.: The Carbohydrate-Fat Ratio in Relation to the Production of Ketone Bodies in Diabetes Mellitus, Proc. Soc. Exper. Biol. & Med. **18**:109, 1921.

(calculated by adding 58 per cent of the protein to the carbohydrate) in the diet of the patients at the point where the ketone body excretion showed a marked increase. In one of our standard diets containing 35 gm. protein, 160 gm. fat and 20 gm. carbohydrate, the corresponding ratio is 1 : 4.

Shaffer [19] who has been studying the relation of the distribution of the foodstuffs burned in different metabolic states to ketosis, has insisted on the importance of the total metabolism in this relation. An outcome of his work is the development of a formula by means of which one may derive the amount of carbohydrate that must be given in the maintenance diet of an aglycosuric diabetic to prevent ketosis. The formula is as follows:

$$\frac{\text{Total Calories}—(100 \times \text{Urine N})}{50} = \text{C. H. in food.}$$

If this formula is applied to our diets, it will be seen that a maintenance diet containing 55 gm. protein, 220 gm. fat and about 2400 calories should include 31 gm. carbohydrate to prevent ketosis; our

TABLE 22.—CARBOHYDRATE-FAT RATIO WHEN KETONURIA APPEARED (LADD AND PALMER)

Case No.	Gm. Available Carbohydrate	Gm. Fat	Ratio
101	60.0	150.6	1 : 2.5
102	25.1	111.0	1 : 4.4
103	40.9	80.4	1 : 1.9
104	31.4	140.1	1 : 4.5
105	25.4	80.5	1 : 3.2
106	25.6	80.1	1 : 3.2
107	51.6	235.3	1 : 4.6
109	28.0	129.9	1 : 4.0
110	36.6	84.1	1 : 2.3

diet containing these amounts of protein and fat does in fact contain 35 gm. carbohydrate. In a similar manner, a patient weighing less may be maintained in nitrogen and caloric balance on a diet containing 35 gm. protein, 165 gm. fat, 25 gm. carbohydrate, 1725 calories; the combustion without ketosis of these amounts of protein and fat would, according to Shaffer's formula, require 23 gm. carbohydrate. Shaffer's fundamental analysis of the mechanism of acidosis, fully justifies the use in practice of these high fat diets.

The important conclusion to be derived from our experience with these 190 cases is that the fear of the use of fat in the treatment of diabetes mellitus is exaggerated, and that fat may be used, as we have used it, without danger of acidosis. On other hand, we do not want to insist on the employment of the exact proportions of the foodstuffs that we have used. It is possible that other combinations may

19. Shaffer, P. A.: The Ketogenic-Antiketogenic Balance in Man, and Its Significance in Diabetes, J. Biol. Chem. **50**: (Proc.) XXVI, 1922.

have their advantages in individual cases. The essential fact is that diabetics can tolerate without acidosis low protein maintenance diets containing four times as much fat as carbohydrate.

Advantages of Limitation of Protein.—In the dietetic treatment of any disease over a long period of time it is of prime importance that nitrogen balance be maintained. We have demonstrated in a previous communication [5] that nitrogen balance can be maintained in the diabetic, as in the normal, by the use of a diet containing 0.67 gm. protein per day per kilogram of body weight, provided enough total calories are given to satisfy the metabolic needs. Protein much in excess of this minimum not only is not a necessity but is a disadvantage, for two reasons. As the protein content of a diet is decreased, the carbohydrate content may be increased without changing the glucose equivalent of the diet. Furthermore, with the decrease in the protein, there is a decrease in the fatty acids, and the food fat, with its greater energy value, may be increased without change in the ratio between the fatty acids and the glucose. For example, in a patient whose total glucose tolerance is 100 gm., either of the diets shown in Table 23

TABLE 23.—CALORIC CONTENT OF DIETS EQUIVALENT IN GLUCOSE

	Protein	Fat	Carbohydrates	Calories	Fatty Acids	Glucose
1.....	150	130	0	1,770	186	100
2.....	50	180	55	2,040	185	100

may be fed without exceeding his glucose tolerance or changing the fatty acid content. The gain in calories is 270. In the second place, the specific dynamic action of the large amount of protein in the first diet causes a much larger increase in the expenditure of enrgy in excess of the basal rates than is caused by fat or carbohydrate, and thereby increases the inadequacy of the diet for maintenance. Recently Wilder, Boothby and Beeler [20] have found that high protein diets increased the basal metabolic rate of a diabetic patient as well as the post-absorptive rate. Wilder [21] believes that an excess of protein exerts a specifically depressant effect on the ability of the organism to utilize glucose.

Total Caloric Content of the Diet.—Besides the proportions of the individual foodstuffs in the diet, it is important to consider the total metabolism. This can conveniently be done by taking up the question under two heads, agreeing with the two phases of treatment: first, the period of desugarization, and second, the prolonged period of after treatment.

20. Wilder, R. M.; Boothby, W. M., and Beeler, C.: Studies of the Metabolism of Diabetes, J. Biol. Chem. **50**: (Proc.) XXVIII, 1922.

21. Wilder, R. M.: Optimal Food Mixtures for Diabetic Patient, J. A. M. A. **78**:1878 (June 17) 1922.

Desugarization Period.—It is important to know whether desugarization is best accomplished by fasting, on the one hand, or by a submaintenance diet, on the other. As has been pointed out, fasting is not ideal for this purpose. A small proportion of patients die as the result of it; it does not always succeed in controlling glycosuria and acidosis; in some cases the fast must be terminated because of an increasing acidosis; and in all cases it is exhausting and a hardship for the patient. We have shown that in our series of adult cases a diet containing 15 gm. protein, 90 gm. fat, 12 gm. carbohydrate and 960 calories has been uniformly successful in eliminating glycosuria and acidosis, without causing any deaths, and without great exhaustion of the patient. Among fifteen children less than 15 years of age treated by similar diets, none has failed to become sugar free, and none has developed an acidosis.

Fasting was introduced for the purpose of decreasing the work of that part of the pancreas that has to do with the intermediary metabolism of the food stuffs. Before accepting this method with its disadvantages it is important to analyze the effect of fasting on normal subjects. For this there is available a large collection of data. The fasting subject continues to require fuel for heat and energy, and derives this from his own tissues. Benedict,[22] for example, has analyzed the nature of the tissues used for this purpose; his subjects burned on the third day of their fast an average of the following amounts of the food stuffs per kilogram of body weight; protein, 1.28 gm., fat, 2.54 gm. and carbohydrate, 0.36 gm. A man weighing 60 kg. may, therefore, be expected to burn 77 gm. protein, 152 gm. fat, 22 gm. carbohydrate, and 1820 calories.

In a general way, the fasting diabetic utilizes his body tissues in the same manner. There will be some variations in the actual proportions of the material burned from patient to patient because of differences in capacity for burning carbohydrate and differences in the ratios of fat to protein in the body. If body fat is available, the patient will derive most of his calories from its combustion. Voit [23] has shown that a well nourished dog which during starvation burned 96 gm. of body fat, burned 97 gm. when fed 100 gm. fat. That is, the same amount of fat was burned, whether it came from his food or from his body. If, on the other hand, the subject is lean, more protein and less fat will be burned. A diabetic who has consumed most of his fat stores is thrown back on his body protein for his important source of energy. He may be spared some of this excessive

22. Benedict, F. G.: Influence of Inanition, Carnegie Inst. Washington, D. C., Pub. 77, p. 476, 1907.
23. Lusk, G.: Science of Nutrition, Philadelphia, 1919.

endogenous protein metabolism by the addition to his metabolic mixture of ingested fat. In the well nourished diabetic, the food fat merely replaces part of the body fat that would be burned in fasting; in the lean diabetic the ingestion of fat permits the same sparing of protein which occurs in fasting in the well nourished diabetic because of the presence of fat stores. In our desugarization diet some of this endogenous protein is replaced. It is not certain that replacement of all protein would not have further advantages. The important fact to be derived from these considerations is that the starving subject continues to burn material, and in amounts not much smaller than when he is resting on a maintenance diet. The amount of relief for the pancreas by fasting must be relatively small. Not only does a diet containing 900 or 1000 calories not increase the work of the pancreas as regards internal secretions, but it may, perhaps, decrease it because it spares protein with its specific dynamic action on the metabolic rate.

We have cited examples of diabetic patients who did not become sugar free when fasted, but who did become sugar free when fed diets containing 900 calories derived chiefly from fat. That this might be predicted from the laws of metabolism has been pointed out by Woodyatt [16] and by us.[5] The lean diabetic who can burn little glucose and whose small residue of body fat supplies but little fuel is of necessity thrown back on his body protein for the production of heat and energy. This protein behaves in a manner no different from that of ingested protein; 58 per cent. of it is converted into glucose. Because of the excessive destruction of body protein, glucose accumulates in the bood, hyperglycemia results, and the urine continues to show sugar. While this phenomenon, which at first glance appears paradoxical can easily be explained, it has been so completely disregarded in the past that it must be strongly emphasized. Protein derived from the tissues is just as capable of producing glycosuria as is protein assimilated from the intestinal tract.

The destruction of important body tissues during fasting cannot be ignored. Table 24 presented by Lusk [23] from the work of Kumagawa, shows the loss of weight of different organs of a dog during a twenty-four day fast. It is interesting to note that the greatest percentage of loss was in the pancreas. May it not be true that more harm than good is done? At any rate the damage to vital organs is not negligible.

A diet of 900 to 1000 calories derived chiefly from fat is devoid of most of the disadvantages of complete fasting for purposes of desugarization. It might be argued that such a diet has disadvantages of its own greater than those of the fasting method. It might be assumed that such a diet does not produce the depression of metabolism

which results from starvation, that it on the contrary causes an increase in the metabolic rate and that it adds glucose to the body.

Data of the fall in basal metabolic rate of normal men due to fasting are available. Examination of Table 25 will show that a fall of less than 10 per cent. of the total heat production of the first day occurred in five days. Unfortunately we have been unable to find enough studies of the effect of fasting on the basal metabolic rate of diabetics to justify any general statement. During five days of fasting, the basal metabolic rate of Cyril K.[24] fell from 40.8 to 35.9 calories per square meter per hour—a decrease of 12 per cent. Studies of the metabolic rates of our patients have shown that there is a rapid fall in the metabolic rate, and that this fall is at least as great as that which may be expected from fasting.

TABLE 24.—Loss in Weight of Different Organs During Starvation (Kumagawa)

Organs	Fat-Free Animal Contains in Percentage of Weight		Fresh Fat-Free Organ Loses in Percentage Weight During a 24 Days' Fast
	Well Nourished	Starvation	
Skeleton	14.78	21.50	5
Skin	10.50	11.29	28
Muscles	53.77	48.39	42
Brain and cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is true, that the diet must cause some slight rise in the metabolic rate above basal. Since most of the energy, however, is derived from fat with its very low specific dynamic action, this rise is negligible.

The small amount of carbohydrate in the diet is compensated for by the decrease in glucose derived from protein consequent to the decrease in protein metabolism.

Period of After Treatment.—Prolonged undernutrition has been advocated for rest of the weakened function of the pancreas. The disadvantages of this method have been pointed out. Its advocates believe that the resultant depression of the total metabolism stays the downward progress of the disease and even improves the carbohydrate

24. Geyelin, H. R., and DuBois, E. F.: Case of Diabetes Mellitus of Maximum Severity, J. A. M. A. **66**:1532 (May 13) 1916.

tolerance in severe cases. It is undoubtedly true that the average duration of life of the diabetic has been increased materially during the last decade. It is impossible, however, to determine how much of this improvement has been due to undernutrition and how much to the increased interest in the disease, the more accurate measurement of the patient's food and his more thorough instruction in dietetics, consequent to the brilliant animal experiments of Allen and the painstaking clinical studies of Joslin. The demonstration that undernutrition is more effective in preventing downward progress and is more liable to improve carbohydrate tolerance than any other diet that keeps the patient aglycosuric has not been made. If it is true that a maintenance diet that will control glycosuria and acidosis will be as successful in the management of the disease as is undernutrition, it is apparent that the former is far more satisfactory than the latter. As has been pointed out, sufficient time has not elapsed for us to answer this

TABLE 25.—Effect of Starvation on Total Metabolism (in Calories)

	Day					Percentile Fall on Fifth Day
	1	2	3	4	5	
"L" [25]	1,834	1,845	1,820	1,760	1,732	5.4
B. F. D. [23]	2,109	2,103	2,110	.....	.....	...
A. L. L. [23]	1,956	2,174	2,056	1,971	.....	...
S. A. B. (III) [22]	1,706	1,772	1,831	1,775	1,655	6.2
J. A. [26]	2,220	2,102	2,024	1,992	1,970	11.0
Cetti* [27]	1,618	1,618	1,618	1,618	1,504	7.1

* Average for periods.

question finally, but it is true that we have not as yet observed loss in tolerance in patients who have adhered to the diet as long as three years. The statistical study of our patients does not show a decrease in the duration of life when compared with other patients who have been treated for the same length of time by undernutrition.

CONCLUSIONS

A diet of 900 calories derived chiefly from fat produces the same fall in basal metabolic rate as does fasting. It has advantages over fasting in that it is more successful in desugarization and is a far less dangerous method.

A low protein, low carbohydrate, high fat, maintenance diet fed a large group of diabetic patients since March 1, 1918, maintained an

25. Benedict, F. G.: A Study of Prolonged Fasting. Carnegie Inst. Washington, D. C., Pub. 103, 1914, p. 414.

26. Landergren, Souden and Tigerstedt: Skand. Arch. f. Physiol. **7**:54, 87, 1897.

27. Lehmann, C., and Zuntz, N.: Untersuchungen an Zwei hungernden Menschen, Arch. f. Pathol. Anat. **131**: (Suppl.) 209, 1893.

aglycosuric state; was not attended by acidosis; maintained nitrogen balance; did not cause a hyperlipoidemia and was attended by its disappearance in those patients in whom it was present at entrance; supplied sufficient energy to avoid the evils of undernutrition and to permit an amount of activity compatible with earning a livelihood; and was, within the limits of our observation not attended by downward progress in uncomplicated cases.

A STEM-STATURE INDEX

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The ratio of the stem-length, i. e., the sitting-height measured in a special and seemingly more accurate manner, to the stature is thought worth bringing to the attention of clinicians for the following reasons:

1. The proportional sitting-height (100 Si ÷ H) has an established value among investigators of growth in school children and, indeed, in general, among physical anthropologists.

2. The absolute measurements of sitting-height and the similar stem-length have been shown in the last six years to possess a notable parallelism to the body weight.[1-5] Some have even believed this correlation to be closer than of weight to height.[1, 2] At least, it seems fair to urge those who take any measurements to include the stem-length.

3. The relationship of body trunk to extremities has, in the last three years, increasingly been brought forward by American physicians in regard to endocrine disease, especially of the hypophysis. This relationship may, in our opinion, be best expressed by a stem-stature index (λ: H). Such a proposition has the following advantages: (a) simplicity, since fewer measurements are needed than with the existing methods to be cited; (b) speed, for the same reason; (c) accuracy, since of the measurements heretofore suggested the stem has the most definite landmarks and also is the least vitiated by carelessness of position on the part of the subject, as has been indicated elsewhere.[2, 6]

THE STEM INDEX IN ENDOCRINE DISORDERS

Before illustrating the possible utility of this proposition, it will be well to survey the methods advocated by others.

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1. Pirquet, C.: Sitzhöhe und Körpergewicht, System der Ernährung II, Ztschr. f. Kinderh. **14**:211, 1916.
2. Dreyer, G.: Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227 (Aug. 9) 1919.
3. Gray, H., and Root, H. F.: Weight Prediction by the Formulae of Bornhardt, of von Pirquet, and of Dreyer, Boston M. & S. J. **185**:28 (July 7) 1921.
4. Gray, H., and Walker, A. M.: Length and Weight, Am. J. Physical Anthropol. **4**:231 (July-Sept.) 1921.
5. Gray, H., and Edmands, G. H.: Indices of the State of Nutrition in Children, Am. J. Dis. Child. **23**:226 (March) 1922.
6. Gray, H.: Sitting-height and Stem-length in Private School Boys, ibid. **23**:406 (May) 1922.

In 1912, Cushing's authoritative monograph [7] on the pituitary body affirmed that "the rôle of the hypophysis in growth is of primary interest." Such measurements, however, as were there reported shed little light on the proportional trunk to limb ratio under discussion. Other writers, too, have evidently thought a ratio not worth consideration, but surely it is worth considering until it shall be either confirmed or condemned.

In 1913, Friedenthal [8] displayed an elaborate geometric scheme, including the skull height, neck length and Rumpflänge, which together he considered not very accurately equal to the sitting-height. If we add his figures we can get 53.7, 17.7, and 12.4 respectively, which total 83.8 cm., and this divided by the average European height, 170 cm., yields 49 per cent. for an index.

In 1913, Tandler and Grosz,[9] while discussing eunuchoidism, gave values for Unterlänge, Oberlänge, and height. As we have not discovered their technic we cannot compare their results strictly with others, but from the last two of their measurements we reckon an index (from their Figures 7, 8, 9 and 13) as varying from 41 to 45 and averaging 43.5 per cent. This shows clearly the relative overgrowth of leg which they commented on in gonadal insufficiency.

In 1916, Falta and Meyers [10] talked of the upper length as distance vertex to symphysis pubis (here to be abbreviated VSY), and the lower length variously as (a) symphysis to heels, or (b) anterior superior spine to internal malleolus, or (c) anterior superior spine to the floor. No normal numerical index was there offered. In their Observation 33, a subject with dyspituitarism, values were given from which the ratio VSY : H may be calculated as 35 per cent., a value agreeing with modern ideas of long legs in anterior lobe hyperfunction such as acromegaly.

However, the pubis is too movable a landmark, as we have shown previously.[4] This source of error receives support in a letter from a well known professor of neurology who has written on certain of these endocrine troubles. He says: "We do not believe that a few centimeters make very much difference. The measurements are taken merely to get the general proportions." In other words, he has noticed that the measurements as taken by some are apt to be a few centimeters in error. In fact, one of the papers cited gives lengths from

7. Cushing, H.: The Pituitary Body, Philadelphia, 1912.
8. Friedenthal, H.: Ueber Wachstum, Ergebn. d. inn. Med. **11**:688, 1913.
9. Tandler, J., and Grosz, S.: Die biologischen Grundlagen der sekundären Geschlechtscharaktere, Berlin, 1913.
10. Falta, W., and Meyers, M. K.: Ductless Glandular Diseases, Ed. 2, Philadelphia, 1916, p. 10.

vertex to pubis and from pubis to floor whose sum differs from the total height by at least 2.5 cm. in all of the four subjects reported, and in two of them by even 3.5 cm. Furthermore, the sum was greater than the height in two of the instances and in two was less, i. e., the error was not even constant in direction. Our own measurements to the symphysis have shown similar irregularities and, therefore, in our judgment bar the pubis as a landmark, convenient though it is to have the normal ratio an even 50 per cent.

In 1919, Timme [11] wrote:

> The bony structure in the first and second stages usually shows . . . anomalies in proportionate skeletal growth, i. e., legs too long for thorax or vice versa. My scale for this determination is a fraction with the numerator as the distance from the sternoclavicular junction to the anterior superior spine of the ilium of the same side, and the denominator the distance from the anterior superior spine to the external malleolus; normally, this fraction is one-half—a larger one meaning too large a torso, while less than one-half represents too long a leg; I call this ratio the torso-leg ratio.

In 1920, Engelbach [12] and Tierney [13] likewise figured a 50 per cent. torso-leg ratio, but with different landmarks. The upper measurement was taken from the top of the vertex, with the spine straightened out, to the top of the symphysis, with the patient in lying position. The "lower measurement" was taken from symphysis to sole.

In each of two cases of thyroid deficiency this ratio was 50 per cent., i. e., normal.

In five cases of hypopituitarism the range was from 48 to 51, averaging 49.6 per cent.; indicating slightly longer legs than normal.

In two cases of hyperpituitarism the ratio came out 47 and 49, with an average of 48 per cent. This agrees with the usual expectation of long legs in acromegaly due to hyperprepituitarism.

In one classical eunuchoid with ovarian insufficiency the ratio was 46 per cent. This conforms to the principle noted by Tandler and Grosz and to the indices we have calculated above from their data.

In 1920, Wilder [14] discussed the difficulty of measuring leg length: "In the leg there is no definite landmark to use as the proximal limit . . . It is usual to consider the head of the femur as marking this limit, but here the difficulty is that this feature lies too deeply for palpation, or even approximately locating it."

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11. Timme, W.: A New Pluriglandular Compensatory Syndrome, M. Clinics N. America **2**:963 (Jan.) 1919.
12. Engelbach, W.: Endocrine Amenorrhea, M. Clinics N. America **4**:665 (Nov.) 1920.
13. Tierney, J. L.: The Basal Metabolic Rate in Endocrine Disturbance, M. Clinics of N. America **4**:775 (Nov.) 1920.
14. Wilder, H. H.: A Laboratory Manual of Anthropometry, Philadelphia, 1920.

Since these things are so for an expert, how much truer for us physicians who practice anthropometry only on the side?

In 1921, Draper,[15] in his turn, practiced still another rule. His trunk length seems to correspond to stem-length. His technic is not detailed in the published paper, but seems of likely interest to any one working on this problem and is therefore quoted from a letter:

> In answer to your questions I may say that I have been somewhat dissatisfied in my own mind about the correctness of measuring the relation of trunk and body length by taking either the umbilicus or the symphysis as the point of division. I have been measuring as nearly as possible the actual length of the trunk and the actual length of the lower extremity. I have done this in the following way: By palpating the upper margin of the trochanter of the femur, and measuring from about a centimeter above this to allow for the slightly higher point of the head of the femur. From this I measure to the sole of the foot in one of two ways: either with the patient recumbent using an architect's T-square, hooking the cross piece under the foot and marking the trochanter point on the long arm of the T-square, or having the patient stand up against the wall and marking the trochanter point in the old-fashioned way against the wall. This gives the actual length of the lower extremity, at least in terms of its bone, which is what you are really after. In measuring the trunk I have felt that the actual information wanted was the distance from the tuberosity of the ischium (the point you really sit on) to the top of the head. This can be measured either by having the patient sit upon a hard stool with his back to wall or standing with his back to the wall and raising one thigh to the right angle position, then feeling for the tuberosity and making a mark on the wall; or you can do it also in a recumbent position with surprising accuracy by measuring from the same trochanter point used for the lower extremity measurement, to the top of the head. To this measurement must be added an average of ten or eleven centimeters because the acetabulum lies about that distance above the tuberosity.
>
> The contours about the waist, hip, and thigh are often very misleading and so-called apparently long-waisted individuals actually measure out the other way and vice versa.

The normal torso-leg ratio he supposed to be about one to one.

In three cases of gonadal insufficiency which he reported, we figure the ratio as from 51 to 52, averaging 51.3 per cent., indicating rather short legs, which is contrary to the usual observations, as noted above.

In two cases with hyperovarian disease the ratio was 53 and 54 per cent. Here the short legs are what we should expect as the converse of Tandler and Grosz's long legs in castrates.

In 1921, Weisenburg and Patten[16] described a most systematic method for the investigation of pituitary disorders. For their torso-leg ratio, normally 1:2, as was the case with the different measurements of Timme, these writers took the distance from the suprasternal notch to the anterior superior spine (average, if different on the two sides),

15. Draper, G.: Reversive Sex Phenomena, M. Clinics N. America **4**:1345 (March) 1921.

16. Weisenburg, T. H., and Patten, C. A.: Methods of Investigation of Pituitary Disorders, M. Clinics N. America **5**:759 (Nov.) 1921.

and from that spine to the internal malleolus. In their six dyspituitarism cases the ratio ranged from 45 to 67 per cent., with an average of 52, i. e., a surprisingly long torso.

Krumbhaar,[17] in 1921, followed the same practice. The ratio in his cases of acromegaly (hyperprepituitarism) was 48 per cent., i. e., a typically short torso.

Recently, Davenport and Love[18] discussed still other landmarks: "The pubic height is important because it is almost exactly (perhaps 35 mm. below) the level of the center of the acetabulum or the axis of the hinge of the femur . . . the length of the physiological leg." Here, again, we wish to insist that the pubic height is unreliable unless measured in a position more firmly defined than we have been able to find in the literature.

> The "leg-length" . . . gluteal fold to internal malleolus . . . is not the physiological leg-length (and) is much less valuable . . . than the total leg-length as indicated by the height of the pubic arch. The leg-length may also be secured by subtracting the sitting-height from the total stature.

These authors found the sitting-height about 53 per cent. of the total height, but laid no great emphasis on this ratio. Incidentally, this proportion differs strikingly from the 50 per cent. reported by most other observers.

Blumgarten[19] in 1922, like Falta and Meyers, took for the lower extremity the distance from the upper border of the pubis to the ground, and for the torso subtracted this distance from the height. In normals he found the torso less than the lower extremities.

The only acromegalic subject of whom we ourselves obtained measurements yielded the $\lambda : H$ index of 55 per cent., which is atypically above the 52 per cent. which we show elsewhere to be normal. In other words, we found, like Weisenburg and Patten, that pituitary patients may have relatively short legs, contrary to what seems to be the rule, judging, for example, Falta and Meyers, Engelbach, Tierney, and Krumbhaar.

Since writing the foregoing, a review of 150 titles, mostly case reports on pituitary disease or on giantism with or without acromegaly has revealed thirty-five articles containing measurements of trunk or extremities. In most instances there were no calculations of the ratio of the additional measurements to the stature, much less any normal index,

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17. Krumbhaar, E. B.: Pituitary Disorders, M. Clinics N. America **5**:927 (Nov.) 1921.

18. Davenport, C. B., and Love, A. G.: Army Anthropology, Statistics, Medical Department U. S. Army in World War, Washington, 1921, p. 199.

19. Blumgarten, A. S.: The Rôle of the Endocrines in Common Medical Diseases, M. Clinics N. America **5**:1023 (Jan.) 1922, and personal communications.

and owing to the variety of landmarks which were used the possible conclusions were less conspicuous than they might have been had a uniform method been used. For the sake of greater completeness the references are grouped according to the extra measurement recorded.[20]

THE STEM-STATURE RATIO AND SIMILAR INDICES IN NORMALS

A synopsis of the rival ratios may be seen in the table. For the sake of compactness the following abbreviations have been assembled from the literature, and are listed in dictionary order.

C = cervicale, free end of the spine of the seventh cervical vertebra, the vertebra prominens (Wilder).

H = total height or stature.

IS = iliospinale anterius, anterior ventral spine of the crest of the ilium, old terminology: anterior superior spine (Wilder).

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20. *Sitting Height.*—Virchow: Ztschr. f. Ethnologie **17**:469, 1885. Ammon, O.: L'anthropologie **7**:285, 1896. Papillault, G.: Bull. soc. d'anthrop., S. 4 **10**: 426 (June 1) 1899. Pittard: Personal communication quoted by Roy, P.: Thèse, Paris, Feb. 25, 1903, p. 75. Launois, P. E., and Roy, P.: Rev. neurol. **10**:1054 (Nov.-Dec.) 1902, and Nouv. Icon. **15**:540, 1902, and Compt. rend. soc. biol. **55**:22 (Jan. 10) 1903, and Etudes biologiques sur les geants, Paris, 1904. Pittard, E.: L'anthropologie **14**:463, 1903. Luschan: Ztschr. f. Ethnologie **35**: 479, 1903. Redlich, E.: Wien. klin. Rundschau **20**:489 and 508 (July 1) 1906. Widal and Boidin: Bull. et mém. Soc. méd d. hôp. de Paris, S. 3 **22**:740 (Oct. 13) 1905. Levi, E.: Nouv. Icon. **21**:297 and 441, 1908. Levi, E., and Franchini, G.: Nouv. Icon. **22**:449 (Feb. 5) 1909.

Great Trochanter to Ground.—Virchow: 1885, loc. cit. Brissaud, E., and Meige, H.: J. de méd .et de chir. pratique **66**:49 (Jan. 25) 1895. Hutchinson, W.: Am. J. M. Sc. **110**:190 (Aug.) 1895. Papillault, G.: Bull. et mém. Soc. d'anthrop., S. 5 **3**:393 (May 1) 1902. Buday, K., and Jansco, N.: Deutsch. Arch. f. klin. Med. **60**:385 (June 16) 1898. Launois and Roy: loc. cit., 1902, 1903, 1904. Huchard, H., and Launois, P. E.: Bull. et mém. Soc. méd. d. hôp. de Paris, S. 3 **20**: (Dec. 11) 1903. Levi: loc. cit., 1908. Thibierge, G., and Gastinel, P.: Nouv. Icon. **22**:442 (Feb. 5) 1909.

Great Trochanter to Malleolus.—Papillault: loc. cit., 1902. Wieting, J.: Deutsch. med. Wchnschr. **29**:371 (May 21) 1903. Huchard and Launois: loc. cit. Duckworth, W. L. H.: J. Anat. & Physiol. **41**:30 (Oct.) 1906. Pel, P. K.: Nouv. Icon. **19**:76, 1906. Levi: 1908, 1909, loc. cit.

Anterior Superior Spine of Ilium to Ground.—Fritsche and Klebs: Klin. u. pathol. anat. Untersuchungen, Leipzig, 1884. Marie, P.: Nouv. Icon. **1**:173, 1888. Papillault: 1902, loc. cit. Luschan: 1903, loc. cit. Pel, P. K.: Berl. klin. Wchnschr. **42**:25 (Oct. 30) 1905. Levi: 1908, loc. cit.

Anterior Superior Spine of Ilium to Malleolus.—Sainton, P.: Nouv. Icon. **15**:272, 1902. Hudovernig, C., and Popovits, U. P.: Nouv. Icon. **16**:181 (May-June) 1903. Traschio, G. B.: Atti della soc. romana di antropologia **9**:95, 1903.

Iliac Crest to Ground.—Virchow: 1885, loc. cit. Dana, C. L.: J. Nerv. & Ment. Dis. **20**:725 (Nov.) 1893. Hutchinson, W.: New York M. J. **67**:452 (March 12) 1898.

Top of Symphysis Pubis to Ground.—Tandler, J., and Grosz, S.: Wien. klin. Wchnschr. **21**:277 (Feb. 27) 1908, and Arch. f. Entwicklungsmechanik **27**:35 (Jan. 12) 1909, and **30**: Part II, 236 (June 14) 1910, and **29**:290 (July 12) 1910.

λ = stem-length, vertex to ischial tuberosities (Walker, Dreyer).

Si = sitting-height (Pirquet).

SPH = spherion, lowest point of internal malleolus (Wilder).

SST = suprasternale, the middle of the suprasternal notch in the upper margin of the sternum (Wilder), called by others the jugulum, sternion, incisura sternalis.

SY = symphysion (Wilder), cephalad edge of middle of symphysis pubis.

TRO = trochanterion, a point of some uncertainty and never very precise. It is defined as the highest point upon the trochanter major (Wilder).

V = vertex (Wilder).

In our own series of eighty healthy men, aged 18 to 71 years, mostly 20 to 35, the index 100 λ ÷ H ranged from 48 to 55 and averaged 51.6 per cent. The frequency of each index was as follows:

100 λ/H = 48-49-50-51-52-53-54-55

No. = 3- 5-12-17-18-18- 5- 2 = 80

NORMAL BODY TRUNK INDICES ACCORDING TO DIFFERENT AUTHORS' DEFINITIONS AND OBSERVATIONS

Measurements	Author	Material	Percentage	
			Range	Average
VSY ÷ H	Quetelet, 1871	Belgians	48-50	49
	Gray and Walker, 1921	U. S.	48-52	50
	Davenport and Love, 1921	U. S. soldiers	49.9-50.7	50.5
(Sternoclavicular junction to IS) ÷ (IS to external malleolus)	Timme, 1919	U. S.		50
(SST to IS) ÷ (SST to IS + (IS to SPH)	Weisenburg and Patten, 1921	U. S.		50
	Krumbhaar, 1921	U. S.		50
Si ÷ H	Friedenthal, 1913	German		49
	Davenport and Love, 1921	U. S. soldiers		52.6
	Baldwin, 1921	U. S. children:		
		Age 6		55.7
		Age 13		52.0
	Gray, 1922	U. S. children:		
		Age 6, 7		54.6
		Age 8 and 9		52.1
		Age 10 and 11		51.3
		Age 12 and 13		51.1
		Age 14, 15 and 16		50.8
		Age 17 and 18		50.0
λ ÷ (λ + TRO to sole)	Draper, 1921			50
λ ÷ H	Gray, 1922	U. S. children:		
		Age 6 and 7		53.7
		Age 8 and 9		51.6
		Age 10 and 11		50.9
		Age 12 and 13		50.0
		Age 14, 15 and 16		49.1
		Age 17 and 18		49.0
	Gray, 1923	U. S. adults		51.6
(H minus distance gluteal fold to SPH) ÷ H	Davenport and Love, 1921	U. S. soldiers		58.3

THE STEM-STATURE INDEX AS A GAGE OF STAMINA IN VARSITY OARSMEN

We have been interested in the belief credited to Ruschenberger of the U. S. Army by Hitchcock [21] in 1893, that the length of the cerebrospinal column may be more dependable than total stature in estimating physical vigor. Ruschenberger conjectured that, as a rule, men of average height made up of a long trunk and comparatively short legs possess greater endurance for labor and exposure to vicissitudes of all kinds than men with comparatively long legs and short trunk.

In order to illuminate this question, we hit on the notion of measuring men of superior sturdiness, irrespective of mere strength or beauty of build. Rowing men seem to us to fulfill this requirement. Among our eighty normals, therefore, are included thirty-six oarsmen,[22] nearly all measured at the Harvard crew quarters at Red Top in June, 1921. Their average index was 51.3, against 51.8 for the forty-four noncrew controls. The difference, 0.50, seems insignificant. However, such small differences are sometimes legitimately regarded as significant when analyzed by the modern biometric methods of Karl Pearson's school. Now then the probable errors, 0.1679 and 0.1655, for the respective means (m1 and m2) just given can be substituted in the formula: $P_{m1\text{-}m2} = \sqrt{(P_{m1})^2 + (P_{m2})^2}$ thus finding the probable error of the difference ($P_{m1\text{-}m2}$) to be 0.236. Now the difference (m1-m2) of 0.50 is only 2.1 times this, its probable error, and is, therefore, hardly significant. In other words, stamina is apparently unrelated to a relatively long trunk. It is still possible that a larger series might show a difference 2.5 times the probable error, in which case the conclusion would be permissible that a man with relatively long legs is more apt to be a fit oarsman than a man with a long trunk—contrary to our original notion.

SUMMARY

The ratio of the stem-length (or the sitting-height) to the stature is thought to be worth consideration by clinicians.

This stem-stature index and other torso-leg ratios are discussed with reference to skeletal anomalies in diseases of internal secretion.

This λ : H index is also tested as a possible measure of stamina.

32 The Fenway.

21. Hitchcock, E.: The Anthropometric Statistics of Amherst Coll., Quart. Pub. Am. Statistical Assn. **3**:596 (Dec.) 1893.

22. For the measurements on the crew men I am greatly indebted to Dr. George P. Denny.

ALBUMINURIA: ITS CLINICAL SIGNIFICANCE AS SHOWN BY CHEMICAL STUDY OF THE BLOOD*

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Although many tests of kidney function have come into prominence and waned to insignificance, albuminuria has long been a simple criterion of abnormality. But albuminuria is not a sure indication of damaged kidneys; for it may appear when these organs are normal, as in orthostatic albuminuria,[1] or it may be absent in a wide spread degeneration of the kidneys, as in interstitial nephritis. Furthermore, as will be pointed out in this paper, albuminuria may be excessive from passive congestion of the kidneys, the primary difficulty being in the heart. When albuminuria is excessive and associated with oliguria and apparent uremia,[2] as a late event in arterial hypertension, or in circulatory failure, it may cause much apprehension; on the other hand, the absence of albumin in the urine may give a false sense of security.

The nephroses of acute infection or resulting from focal infection, are associated with albuminuria,[3] more or less severe; the damage may be transient, fulminating or permanent.[4]

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* Albuminuria as here referred to is associated with casts in varying abundance. Albuminuria resulting from pyonephrosis or inflammatory conditions in the urinary tract are not considered, since their recognition is obvious.

1. One observer estimates the frequency of orthostatic albuminuria as high as 19 per cent. in adolescents, many losing this tendency as they grow older.

2. Attention is directed to uremic symptoms resulting from cerebral edema, the latter being due to circulatory changes largely, and disappearing on adequate cardiac stimulation, as shown in a woman, aged 52, who had been stuporous and semicomatose for eight days with marked albuminuria and oliguria. Lumbar puncture showed increased pressure and a high urea content of the spinal fluid. The removal of spinal fluid and stimulation for the dilated, uncompensated heart seemed to start recovery. She was well for five years and died of intercurrent carcinoma of the stomach; during this period there was very little evidence of kidney involvement. That edema of the brain may occur in uremia is stated by N. B. Foster (Uremia, J. A. M. A. **76**:281 [Jan 29] 1921) as follows: "In its greatest severity edema of the brain occurs in but one type of uremia, that type in which stupor and coma without convulsions, without psychic or motor disturbances, is the prominent nervous symptom." For a clear discussion of uremia, as modernly understood, and cerebral edema, the reader is referred to Foster's paper.

3. George Baer and H. Lande (Glomerulonephritis as a Complication of Subacute Streptococcus Endocarditis, J. A. M. A. **75**:789 [Sept. 18] 1920) report twenty-seven cases of subacute streptococcus endocarditis in which nine patients died of uremia due to intercurrent glomerular nephritis or its sequel, chronic diffuse nephritis. They found that scarlet fever, acute and chronic streptococcus angina and streptococcus endocarditis are frequently complicated by acute glomerular nephritis.

(Footnote 4 on next page)

Nonnephritic albuminuria,[5] including "physiologic," "transient," "functional," "adolescent," "intermittent" and the albuminuria in pregnancy, etc., is a large group comparatively easy of detection. The difference between physiologic and pathologic albuminuria is quantitative, not qualitative, and the term "albuminuria" implies that serum albumin is present in the urine in such quantities that it can be detected by the not very delicate tests accepted as standard (as the heat and acid test).[6]

From the foregoing, it is readily seen that dependence on urinary findings alone leads to error. Furthermore, as stated by McLester,[7] many persons show albumin and casts in the urine for years, without any other signs of nephritis, while at the same time, they demonstrate their ability to withstand, without injury, all kinds of fatigue and hardships. Such people cannot be said to have nephritis. He also points out that chronic nephritis can be divided sharply into two groups; (1) the type with edema, and (2) that without edema. The latter is not a disease of the kidneys alone, for in the resulting disturbed physiology, other organs, notably the heart and arteries, play an equally important part; and in the last analysis it is the efficiency of these other organs which determines, as a rule, the fate of the patient.

RENAL FUNCTION TESTS

Discussion of albuminuria leads to a consideration of renal function. In attempting to explain the albuminuria as seen in the cases cited below, various methods which have been used in the last decade were reviewed

4. Eli Moschowitz (Hypertension; Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, Am. J. M. Sc. **168**:668 [Nov.] 1919) is of the opinion that gross injury of the kidney parenchyma perhaps plays the greatest rôle in albuminuria of the acute infections, but that it (injury of the parenchyma) is not a factor of much importance in albuminuria associated with hypertension and also points out (ibid. p. 684) that albuminuria is not necessarily the result of injury (even profound) of the kidney and that badly diseased kidneys may show no albuminuria.

5. R. L. M. Wallis (Nonnephritic Albuminuria, Proc. Roy. Soc. Lond., Sect. Med. **13**:96, 1920), in discussing proteinuria not due to organic disease of the kidney, including physiologic, transient and intermittent albuminuria, and a group he designates as "leaky kidneys," points out that all ordinary tests for albumin are for serum albumin. In the group under discussion, the chemical examination of the blood shows no retention. Physiologic albuminuria is the result of serum albumin leaking through the kidneys, with excessive amounts of urinary constituents (after exercise, cold baths, alimentary causes, etc.). In functional albuminuria there is no relation to food or exercise as seen in adolescent, cyclic and postural albuminuria. A third group of "leaky kidneys" is a long standing proteinuria, and there is no evidence of kidney disease, or if present, it is not progressive. The chief protein in nonnephritic albuminuria is euglobulin associated with lipoids.

6. Emerson: Clinical Diagnosis, J. B. Lippincott, 1921, p. 224.

7. McLester, J. S.: Treatment of Chronic Nephritis Without Edema, J. A. M. A. **77**:88 (July 9) 1921.

and used to some extent. Methods using the urine alone as the object of examination were found to be disappointing, the chemical examinations of the blood along with a renal test diet being found most valuable in determining the state of kidney function.

Normal renal function depends so largely on the volume of blood passing through the kidneys, that they respond readily to blood flow and blood pressure. These organs differ from all other secreting glands in their intimate relation to the general circulation; a rise in blood pressure is accompanied by an increase in urine flow unless there is a simultaneous vasoconstriction in the kidneys; and a fall in blood pressure is followed in general by decreased urine flow unless the renal vessels are dilated. The determining factor is the capillary pressure in the glomerulus—not the general vascular pressure.

The modern view of secretion of the urine accepts Ludwig's [8] scheme of filtration through the capsules and the "vital secretion" of Heidenhain. Filtration is purely physical; reabsorption in the tubule requires a healthy cell. The function of the kidney is the filtration of noncolloidal constituents of the blood through the glomerulus and absorption of this fluid through the tubule cells; the capsule furnishes fluid as it is the circulation and the tubule returns to the blood the fluid best adapted to the tissues,[9] allowing the rest to escape in the urine.[10]

Albuminuria may be produced experimentally by interrupting the blood supply by compressing vein, artery or ureter. If the artery is clamped for thirty seconds, secretion stops completely and is reinstated after an hour or so; the urine contains abundant protein at first and ultimately resumes its normal character. This is due to alteration in the permeability of the capsule by asphyxia so that it permits the passage of the proteins of the blood.

Since the urine is the excretory product of renal activity, estimation of renal function has been attempted through urine tests. Estimation of urinary nitrogen, chlorids, diastase, urea, uric acid, the power of the kidney to eliminate foreign substances, cryoscopy, its electrical conductivity, experimental polyuria, etc., have been disappointing, for the elimination of urine is complicated, depending on many factors beyond

8. Cushny, A. R.: The Secretion of the Urine, London and New York, Longmans, Green and Co., 1917, p. 101.

9. Cushny, A. R.: The Secretion of the Urine, New York, Longmans, Green & Co., 1917, p. 47.

10. According to Cushny, casts are chiefly composed of albumin passing through the kidney capsule, enriched by the detritus of degenerating tubule cells, but Christian (Am. J. M. Sc. **161**:625 [May] 1916) thinks they originate from degenerated epithelium, the granular being young and the hyaline older.

accurate control, such as the state of circulation, food and fluid intake, and psychic and nervous conditions.[11]

Following the work of Schlayer [12] and others who attempted clinically to classify nephritis as tubular, glomerular and vascular (through the readiness with which water and lactose pass through the glomeruli, and potassium iodide and sodium chloride through the tubules), many attempts were made to make clinical and histologic nephritis conform. These have failed to give adequate information, and even Ambard's coefficient (the relation between urinary and blood urea) is unsatisfactory because of these variable factors in urine elimination. Further, the disease process in the kidney is rarely confined to one structure, but is diffuse.

The excretion of dyes (methylene blue, indigocarmine, phenolsulphonephthalein, etc.), offers a simple clinical method of estimating renal activity, but here again one must bear in mind the many factors concerned in their elimination, and that prostatic obstruction or passive hyperemia of the kidneys may produce a low excretion of these substances.[13]

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11. The readiness with which the kidneys eliminate an excess of any urinary constituents is utilized in giving urea, 15 gm., while the diet is kept fairly constant and the rate and amount of excretion is measured as described by Addis, McCaskey, McLean and De Wesselow. Recently Weiss (Weiss, E.: The Urea Concentration Test for Kidney Function, J. A. M. A. **76**:298 [Jan. 29] 1921) has added to this the estimation of the blood urea nitrogen with a review of the literature. Uric acid has been used in the same way by Upham and Higley and Magath. More recently T. L. Squier and L. H. Newburgh (Renal Irritation in Man from High Protein Diet, Arch. Int. Med. **28**:1 [July] 1921) have used high protein diets, attempting to obtain evidence in hypertension cases of disturbed kidney function by throwing an extra load on the kidneys. This was followed by albuminuria and casts and the presence of red corpuscles in the urine. There was no effect on blood pressure.

12. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med. **114**:120, 1914.

13. Thayer, W. S., and Snowden, R. R.: Comparison of the Results of the Phenolsulphonephthalein Test of Renal Function with the Anatomic Changes Observed in the Kidneys at Necropsy, Am. J. M. Sc. **148**:781 (Dec.) 1914.

J. H. Agnew (A Comparative Study of Phthalein and Incoagulable Nitrogen of the Blood in Cardiorenal Disease, Arch. Int. Med. **13**:485 [March] 1914) stated that when phenolsulphonephthalein was below 40 per cent. the blood nitrogen was definitely increased.

Rowntree and his co-workers (Rowntree, L. G.; Marshall, E. K., and Baetjer, W. A.: Further Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, Arch. Int. Med. **15**:543 [April] 1915) studied diastase, phenolsulphonephthalein, cryoscopy, total nitrogen and urea of the blood, finding diastase low in mild and severe nephritis. In cardiac and cardiorenal cases the findings were bizarre; phenolsulphonephthalein was then thought by them to be the test of choice, but "whenever phenolsulphonephthalein is decreased, even slightly, the total N or blood urea, or both, should be determined."

Renal test diets as suggested by v. Monakow in 1911, Hedinger and Schlayer in 1914 and as modified by Mosenthal,[14] Christian,[15] O'Hare [16] and others offer simple clinical means of estimating renal function through measuring the concentrating power of the kidney.

Mosenthal [14] has now modified his former method based on the observations of Hedinger and Schlayer in 1914, using an American standard diet and only one day of measured diet, covering the period of urine collections. It is applicable to the ambulatory patients and allows usual food and routine. The urine is collected at two hour intervals, only one direction being insisted on, that the night urine be collected at a time beginning three hours after supper and no sooner.

Normal renal activity is characterized by variations in specific gravity up to 1.020 in the two hour test. A high fixed gravity may be

TABLE 1.—RENAL TEST DIET. SHOWING VARIATIONS IN URINE OUTPUT, SPECIFIC GRAVITY, NITROGEN AND CHLORIDS IN NORMAL (N) AND NEPHRITIC (NEPH) URINES (AFTER MOSENTHAL)

	Renal Test Diet							
	Amount, C.c.		Specific Gravity		Sodium Chlorid, Gm.		Nitrogen, Gm.	
Hour	Normal	Nephritic	Normal	Nephritic	Normal	Nephritic	Normal	Nephritic
8-10	315	102	1.006	1.017	....	....	....	....
10-12	128	90	1.014	1.020	....	....	....	....
12- 2	120	98	1.017	1.020	....	....	....	....
2- 4	122	118	1.020	1.021	....	....	....	....
4- 6	76	88	1.022	1.020	....	....	....	....
6- 8	100	390	1.027	1.006	....	....	....	....
Total day	861	886	.....	.....	6.71	3.86	6.80	4.62
Total night	248	1,280	1.025	1.010	1.71	6.26	3.05	4.86
Total 24 hours	1,109	2,166	.....	.....	8.42	10.12	9.85	9.48
Intake	1,760	1,760	.....	.....	8.50	8.50	13.40	13.40
Balance	+650	—406	.....	.....	+0.08	—1.62	+3.55	+3.92

seen in normal persons because they take too little fluid, or may occur in disease characterized by edema and oliguria, as myocardial insufficiency, acute or chronic nephritis. A low fixed gravity is found in chronic nephritis, diabetes insipidus, marked anemia, the elimination of edema, pyelitis, polycystic kidney, postatic hypertrophy, etc. Such patients do well as long as polyuria compensates for the lack of power to concentrate. The normal total quantity should be 400 c.c. less than the intake and 750 c.c. or less is secreted at night; a larger amount may indicate that the kidney is putting forth a greater effort than it

14. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, Arch. Int. Med. **16**:733 (Dec.) 1915; ibid. **22**:770 (Dec.) 1918.

15. Christian, H.: Some Phases of the Nephritis Problem, Am. J. M. Sc. **151**:625 (May) 1916. Tests for Measurements of Renal Efficiency in Relation to Prognosis in Nephritis, Penn. M. J. **21**:233 (Jan.) 1918.

16. O'Hare, J. P.: Renal Function in Vascular Hypertension, Boston M. & S. J. **132**:345 (April) 1920.

normally should. This overstrain may cause damage if continued indefinitely. In passive congestion water and salt are diminished while the nitrogen remains approximately normal. In the contracted kidney nitrogen and salt are retained. Hypertensive nephritis is characterized by nocturnal polyuria, a tendency to total polyuria, fixation of specific gravity, fixation of two hourly quantity and retention of salt and nitrogen (Table 1).

Another avenue of approach in the estimation of renal function is the chemical examination of the blood [17] for retention of substances normally excreted by the kidneys, particularly urea, uric acid, and creatinin. Blood sugar may also be increased in interstitial nephritis.[18] Since creatinin is readily excreted through the kidneys, urea less readily and uric acid least readily, it was shown by Meyers and Killian [19]

TABLE 2.—THE BLOOD IN NEPHRITIC AND CARDIAC ALBUMINURIA. SHOWING NORMAL VALUES FOR NONPROTEIN NITROGEN, UREA, URIC ACID, CREATININ AND SUGAR AS COMPARED WITH FINDINGS IN PASSIVE RENAL CONGESTION OR NEPHRITIS AS SHOWN BY GETTLER, GRADWOHL, MEYERS AND FINE

	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Creatinin, Mg.	Uric Acid, Mg.	Sugar, Mg.
Normal	25-40	10- 15	1-2	1-3	0.08-0.11
Gettler:					
Nephritis (600 cases)	40-400	20-275	2-42	3-17	0.075-0.375
Cardiac (350 cases)	25-250	18-180	15-12	2.5-7	0.07 -0.135
Gradwohl:					
Nephritis (4 cases)	.....	21-108	2.15-4.48	5.9-9.8	0.09 -0.188
Cardiac (4 cases)	.....	11- 16	0.9 -2	2.4-3.3	0.096-0.155
Meyers and Fine:					
Chronic nephritis	30- 80	15- 50	1- 3	1- 4	.....
Uremic nephritis	120-350	80-300	4-34	4-15	0.10-0.20

that a marked retention of blood creatinin is of serious prognostic import. Upham and Higley [20] and Magath [21] and others fed uric acid as a test of renal insufficiency.

17. So much work has been done in this line in the last decade that it is hardly necessary to refer to the investigations of Folin and Dennis, Benedict and Lewis, Meyers and Fine and Christian and others who have opened the way for the clinical application of experimental physiologic chemistry.

18. J. R. Williams and E. M. Humphreys studied fifty cases of cardiorenal disease, finding the blood sugar varying from 0.06 to 0.25 per cent., and varying directly with the severity of the disease. (The Clinical Significance of Blood Sugar in Nephritis and Other Diseases, Arch. Int. Med. **22**:537 [May] 1919.) They quote Hopkins, who in 1915 studied twenty-six cases of nephritis, finding the blood sugar normal in only five; also Meyers and Bailey, who in 1916 studied eleven cases, finding blood sugar from 0.10 to 0.20 per cent.

19. Meyers, V. C., and Killian, J. A.: The Prognostic Value of Creatinin of the Blood in Nephritis, Am. J. M. Sc. **157**:674 (May) 1919. Meyers, V. C., and Lough, W. G.: The Creatinin of the Blood in Nephritis: Its Diagnostic Value, Arch. Int. Med. **16**:536 (Oct.) 1915.

20. Upham, R., and Higley, H. A.: Study of Renal Concentration Power for Uric Acid in Early Chronic Interstitial Nephritis, Arch. Int. Med. **22**:537 (Sept.) 1920.

21. Magath, T. B.: A Test for Renal Insufficiency, J. Lab. & Clin. Med. **6**:463 (May) 1921.

While diseased kidneys interfere with the excretion of these substances, causing them to be retained in the body,[22] passive renal congestion does not do so, as shown in the accompanying tables and case reports, and as pointed out by Gradwohl and Powell,[23] Christian,[24] Williams[25] and others (Table 2).

From the foregoing consideration of various renal function tests, it will be seen that groping, tedious effort and painstaking accumulation of laboratory data have at least given a clearer conception of the difficulties in establishing any one test for kidney efficiency. While most of the older methods of examination of the urine have been given up for reasons already cited, albumin and casts are easily found by any one, and immediately arouse suspicion of disturbed renal activity; they give a clue also as to the degree of this disturbance, but hardly of the extent of damage.

One is often surprised to find that patients who at first suggest the "cardionephritis syndrome" are suffering more from circulatory weakness than nephritis, for oliguria, edema, excessive albuminuria, and even apparent mild uremia improve with improved circulation. Again, patients with arterial hypertension show "nephritic" symptoms from time to time, which are due to myocardial weakness.

In considering the cases studied from the standpoint of albuminuria the following table is submitted for the differentiation of primary (or renal) from secondary (or extrarenal) albuminuria.

1. *Primary.*—With definite evidence of renal insufficiency and probable permanent damage (nephritis).[26]

2. *Secondary.*—Due to extrarenal factors: (*a*) Nonnephritic albuminuria (physiologic, adolescent, functional, etc.), (*b*) in cardiac

22. That nitrogen is not retained exclusively in the blood is shown by N. B. Foster (The Increased Extract Nitrogen in the Tissues, with Chronic Nephritis, Arch. Int. Med. **24**:242 [Aug.] 1919).

23. Gradwohl, R. B., and Powell, C.: The Usefulness of Blood Chemistry Methods in the Differential Diagnosis and Cardiac and Renal Diseases, Southern M. J. **11**:335 (May) 1918.

24. Christian, H. A.: The Use of Renal Function Tests in Cases of Nephritis, J. Urol. **1**:319 (June) 1917.

25. Williams, J. L.: The Total Nonprotein Nitrogen Constituents of the Blood in Chronic Nephritis with Hypertension, Arch. Int. Med. **28**:426 (Oct.) 1921. Williams found that in hypertension and uremia the nonprotein nitrogen was increased and phenolsulphonephthalein excretion decreased. Cardiac insufficiency without nephritis is associated with moderate retention of nonprotein substances of the blood, especially of uric acid. He says the presence of albumin and casts do not necessarily suggest nephritis but that improvement in the circulation is accompanied by decrease in nitrogenous extract in the blood, especially of uric acid.

26. C. P. Emerson (The Acute Element in the Nephropathies, J. A. M. A. **77**:745 [Sept. 3] 1921) considers that nephritis, when well established, is not a chronic process but due to repeated acute attacks. In the albuminuria due to extrarenal factors, especially from passive congestion, it is conceivable that permanent damage may result from repeated attacks.

decompensation with resultant passive congestion (oliguria, edema, uremic symptoms).

1. With valvular lesions (rheumatic, syphilitic, or sclerotic), with myocardial weakness and dilatation.

2. Resulting from long continued vascular hypertension and final cardiac breakdown.

DISCUSSION OF CLINICAL GROUPS

In studying the results of functional tests, and especially of blood chemistry in patients having albuminuria, those with vascular hypertension form one group, and the others have been studied as a miscellaneous group. In the former, the following points stand out: (1) these patients at sometime or other show "cardionephritic" symptoms. It will be seen that albuminuria varies greatly in the same patient, as do other evidences of renal embarrassment, and that there is often a definite relationship between cardiac breakdown and the nephritic symptoms (Table 3). (2) The predominating symptoms in hypertension express themselves as (*a*) cerebral, (*b*) cardiac, or (*c*) nephritic, appearing singly, or jointly. (3) In these patients, the chemical examination of the blood was of diagnostic value.

Some of the hypertension cases have been seen more or less regularly over a period of years (from five to eight). Since making chemical examinations of the blood one has the impression of assurance of the true state of the kidneys which formerly was doubtful.

Uric acid [27] values have been high in some cases, as in 17 K (5.75), 21 J L (5.75, 6.25 and 6.7) and 85 H (4.1), but at such times there was no particular change in the patient's general condition.

The alkali reserve was estimated in seven instances and was not of any particular help in the care of the patients.

Blood sugar was not high, as a rule. Case 29 H showed 0.204 in September, 1919, but there was no glycosuria, while Cases 45 F (0.12) 17 K (0.142 and 0.125) and 14 W (0.14) showed higher values than normal.

REPORT OF CASES

Hypertension Cases with Albuminuria (Table 3).— The following cases illustrate the points that have already been made; some are given at considerable length because they are typical of recurring albuminuria secondary to cardiac decompensation and resultant static changes (passive congestion) in the kidneys.[27a]

27. All chemical methods were standard and done with the helpful advice of Professor Haskins of the Medical Department of the University of Oregon. Blood was obtained in the morning, the patient fasting.

27a. Measurements of enlarged heart are to left of midclavicular line. Quantitative albumin is in parts per thousand by Esbach's method.

TABLE 3.—Hypertension Group. Showing Increase in Albuminuria Often Coincident with Increased Cardiac Embarrassment. Cardiac Symptoms Were Dyspnea, Rapid Pulse, Increased Heart Borders, Cyanosis, Enlarged Liver, Edema, Etc. Cerebral Symptoms Varied from Mental Confusion, Headache, Sclerotic Retinal Vessels, Aphasia or Cerebral Hemorrhage. Nephritic Symptoms Were Oliguria, Marked Albuminuria and Casts, Edema, Uremia Symptoms

Case	Age	Date	Predominating Symptoms			Blood Pressure	Blood Chemistry					Urine		
			Cerebral	Cardiac	Nephritic		Urea	Uric Acid	Creatinin	Sugar	Alkali Reserve	Specific Gravity	Albumin	Casts
45 F	51	4/12/20	.....	++++	+++	210-135	....	....	....	....	..	1.016	+++	+++
		4/14/20	.....	++++	++	210-155	15	2.17	1.4	0.12	..	1.009	0.1%	++
		5/—/20	.....	+	±	195-135	14	2.62	1.17	0.11	..	1.010	±	+
		12/—/20	.....	++++	+++	195-130	16	3.12	2	0.10	..	1.014	0.35%	+++
		2/ 4/21	++	++++	+++	150-110	....	....	....	....	..	1.020	+++	+++
81 S	58	6/—/20	.....	++++	+++	155-125	....	....	....	....	..	1.020	+++	++++
				++	±	170- 90	15	2.75	1.9	0.08	62	1.010	+	
		9/—/20	+++	+	.....	180-140	12.5	1.35	2.2	0.083	72	1.012	+	+
50 C	50	3/—/20	++	++	++	225-150	....	....	....	....	..	1.020	++	++
		6/—/20	+	++	+	250-110	10	2.74	2.43	0.089	70	1.018	++	++
		8/—/20	+++	++	+	250-150	12.5	2.92	2	....	..	1.018	+	+
71 G	74	6/12/20	++	+	++	185-105	....	....	....	....	..	.....	++	+
		6/14/20	.....	.....	.....	.....	13.5	2.5	1.33	0.083	..	.....	0.2%	
6 J	59	5/—/19	+++	±	+	240-120	....	....	....	....	..	1.020	+	+
		7/—/19	+++	±	+	180-165	11	....	1.16	0.09	..	1.020	+	+
17 K	70	8/—/15	+	±	±	280-142	....	....	....	....	..	1.015	±	±
		8/—/19	+++	±	±	225-138	25.5	....	2	0.142	..	1.018	±	±
		1/—/20	++	±	±	220-130	....	2.37	1.17	....	..	1.018	+	+
		6/—/20	+++	±	±	240-135	14.5	....	1.7	0.125	70	1.017	+	+
		8/—/21	+++	++	++	139- 45	30.5	5.75	1.9	0.11	..	1.015	++	+
21 J L	69	4/—/14	+	+	+	205-130	....	....	....	....	..	1.018	+	+
		9/—/19	+	++++	++	190-105	27	....	4	0.10	..	1.013	++	++
		10/—/19	+	+	+	210-125	22.5	....	2	0.12	..	1.012	+	+
		5/—/20	+	+	+	240-130	25	6.7	4	0.11	..	1.012	+	+
		12/—/20	+++	+++	++	190-115	25	6.25	2.5	0.10	75	1.017	+	+
		8/—/21	++	+++	++	135- 95	30.5	5.75	1.9	0.11	..	1.014	+	+
79 R	57	6/—/20	++	.....	.....	210-125	10	2.25	1.81	0.09	..	1.020		
29 H	56	9/—/19	.....	+++	++	195-115	13.5	....	0.08	0.204	..	1.012	0.35%	+++
		10/ 9/19	.....	+++	++	190-125	....	....	....	....	..	1.014	0.275%	+++
		10/21/19	.....	+++	++	.....	32.5	....	3.08	....	..	1.018	0.4%	+++
85 H	50	7/ 3/20	.....	++++	+++	140- 95	17.5	4.1	2	0.11	77	1.024	++	++
		7/10/20	.....	+++	++	155-110	15	3.25	1.5	0.083	65	1.020	++	++
36 G	69	12/19/19	+	+++	++	185-105	....	....	....	....	..	1.026	0.1%	+++
		12/22/19	+	++	+	.....	22	....	1.95	0.07	..	1.022	+	+
20 H	68	8/30/19	+++	+	+++	235-125	....	....	....	....	..	1.020	+++	+++
		8/31/19	+++	+	+++	180-115	....	....	....	....	..	1.022	0.3.5%	+++
		9/ 1/19	+++	+	+++	160-115	99	....	7.4	0.096				
14 W	..	8/ 8/19	+	.....	.....	215-110								
		8/ 9/19	.....	.....	.....	195-105	11.5	....	1.6	0.14	..	1.025	+	+
22 T	..	8/29/19	++	.....	.....	190-125								
		9/—/19	.....	.....	.....	210-125	19	....	2	0.10	..	1.022		

Case 1 (45).—*History.*—J. F., aged 51, seen April 12, 1921, complained of increasing dyspnea and recent orthopnea. He had been aware of some shortness of breath since a severe attack lasting several hours three years ago, when he ran up a long flight of stairs. For six weeks it had been more troublesome, so that he could only walk two blocks when he had to stop and rest, and for three weeks he had been unable to lie flat in bed, requiring three or four pillows. He had no digestive symptoms, edema or cough. He had not given up his business, which was mostly sedentary.

Examination.—Moderate cyanosis, dilated heart (left border 5 cm. to the left, in the sixth space) with moderate systolic murmur at apex, transmitted to axilla, and a softer systolic murmur at the base was noted. There was moderate respiratory effort. Blood pressure, 210/135; pulse regular. Urine passed in the office showed excessive albumin, and many hyaline, fine and coarse granular and cellular casts, no blood.

The picture was that of a cardiac breakdown assumed to be secondary to hypertension of some duration. The urine suggested nephritis and further study.

Treatment.—He was put to bed, given digitalis in sufficient dosage, and when seen two days later he was breathing easier and passing sufficient urine, and there was but a trace of albumin. The chemical examination of the blood is shown in Table 4, revealing practically normal values. From this and the general picture, it was assumed that the kidneys, while in all probability the seat of interstitial change, were embarrassed from insufficient circulation (chronic passive congestion).

TABLE 4.—Results of Examination of Blood of J. F. (Case 1)

Date	Blood Pressure	Urea	Uric Acid	Creatinin	Sugar	Specific Gravity	Albumin	Casts
April 12	210/135	..	....	....	....	1.016	Excessive	Many
April 14	205/130	15	2.17	1.4	0.12	1.010	Trace	Few
May 20	190/135	14	2.62	1.17	0.11	1.010	Trace	Few
Dec. 15	195/130	16	3.12	2	0.10	1.012	Excessive	Many

Course.—The course of the disease seemed to bear this out, for after six weeks of general supervision, he had less dyspnea, the heart borders were nearer normal, and he was able to walk eight blocks without distress. He had required frequent courses of digitalis for recurrent cardiac embarrassment. During these recurrences albumin increased.

In the next five months he was up, and spending some time at the seashore, but with slight unusual effort cardiac symptoms recurred, always attended with increase in the evidences of renal embarrassment, but controlled by rest and digitalis. At one time, the heart dilated to the anterior axillary line, the liver became enlarged and tender, and slight edema appeared at the ankles. December 18 he was again seen in decompensation, the left border of the heart being in the anterior axillary line, the apical murmur loud, and the liver swollen and undoubtedly pulsating. He was given digitalis to nausea; the pulse rate dropped to 40 per minute, and the pulse became bigeminal, improving gradually on withdrawal of the drug and without the use of atropin; polygrams showed heart block. The electrocardiograph was not available then. The urine was much decreased in amount, contained excessive albumin (3.5 gm. per liter in twenty-four hours' urine), and there were numerous casts; indican was excessive, and urobilin moderate. He was definitely jaundiced, and the liver was four and one-half finger breadths below the costal margin.

The course was steadily downward from this time to February 4, when he was mentally confused and so drowsy that he fell asleep while being examined. There was marked cardiac dilatation with dyspnea and Cheyne-Stokes respiration, anasarca; enlarged liver. The urine had cleared up considerably, there being a moderate trace of albumin, and a moderate number of casts of all kinds. He died two days later.

Comment.—This is primarily a case of heart disease throughout the clinical course of nine months, with recurring nephritic symptoms, the latter cleared up with cardiac improvement. At no time until a few days before death did a suggestion of uremia (drowsiness, mental confusion) appear; these symptoms were assumed to be due to cerebral edema, since the urine output was sufficient and albumin and casts had decreased. The patient died of heart failure. There were never evidences of other cerebral insults.

Albuminuria in this case seemed directly associated with cardiac weakness; there were no evidences of retention in the blood. While albumin decreased on the second day after rest and digitalis had been instituted, the practically normal blood values gave a sense of security as to serious damage in the kidneys, and later observations bore this out.

Case 2 (81)—*History.*—C. S., aged 58, a farmer, complained of shortness of breath for over a year, dating back to six years before when he overworked and was laid up with his heart for a month. The amount of twenty-four hour urine, he said, was about 1 quart. He was under a physician's care three months before, when, after a few weeks in bed, he was so much better that he was able to take up light work on the farm. He had had increasing difficulty with breathing, and much swelling of the legs for two weeks.

TABLE 5.—Results of Examination of the Blood of C. S. (Case 2)

Date	Blood Pressure	Urea	Uric Acid	Creatinin	Sugar	Specific Gravity	Albumin	Casts
June 25	155/125	..	....	....	....	1.020	Excessive	Excessive
June 28	160/125	15	2.75	1.9	0.089	1.010	Trace	Few
Sept.	180/140	12.5	1.25	2.2	0.083	1.018	Moderate	Moderate

Examination.—Slightly cyanotic, considerable respiratory effort. The heart was 6.5 cm. to the left of the midclavicular line in the sixth space, the sounds were distant, due to some emphysema; there were no murmurs; blood pressure, 155/125. The arteries were considerably thickened. The legs were markedly edematous, the swelling extending to the abdomen, and there was some ascites. Urine (office specimen) showed excessive albumin, excessive hyaline, large and small granular and few cellular casts, no urobilin.

Treatment.—He was put to bed, diet restricted, and given sufficient digitalis. He had much nausea and vomiting for three days. The urine on the fourth day showed specific gravity, 1.010; trace of albumin; no casts found. The heart was compensating well, and with very little distress; there was but a faint trace of albumin, and no casts. Blood pressure, 170/90; pulse, regular; heart borders, 3.5 cm. to left of midclavicular line in fifth space.

Course.—Two weeks later there was some return of dyspnea and edema, and, after ten days of rest and occasional use of digitalis, he was up and about and steadily improving. Two months later, he had a cerebral hemorrhage with paralysis in the right arm and face. Blood pressure was then 180/140. Urine showed moderate albumin, moderate granular, and few cellular casts. He died in coma two days later. Result of chemical examination of the blood is shown in Table 5.

Comment.—Cardiac symptoms predominated until two days before death, when there was a cerebral hemorrhage. At first nephritic symp-

toms were prominent, but there was no particular blood retention and these symptoms improved with cardiac compensation.

CASE 3 (50).—*History.*—J. C., aged 50, seen first March 26, 1920, complained of occipital headaches for two weeks, which awakened him in the early morning. Headaches formerly were occasional, but for the last few days had been constant and severe. For years he had been a hard worker in a responsible position as manager in a large paper mill.

Examination.—Blood pressure was 225/150. The brachials were moderately thickened; the heart was moderately dilated, but there was no edema or cyanosis. The urine showed a definite trace of albumin, with few casts. There were some infected teeth.

Treatment.—Two weeks later, on restricted diet and rest, his blood pressure was 180/120, and the urine showed a faint trace of albumin; the headaches were less, and he was generally better. June 11 blood chemistry showed: urea, 10; creatinin, 2; uric acid, 2.92; sugar, 0.08. The urine showed definite trace of albumin, specific gravity, 1.018, and a few granular casts.

Course.—August 13 he had sudden dimness of vision of left eye, which was due to edema of the retina. His blood pressure was then 250/150, and remained high in spite of bed rest, diaphoresis, catharsis, etc. September 7, he complained of more headache and was having some anginoid pain in the precordium. In the next six weeks he improved considerably, and left for New York on a business trip where he developed acute pulmonary edema. He was seen by Dr. Frank Meara. After a time he went to Boston, and was seen by Dr. Locke, because he was having shortness of breath, and some edema of the ankles.

His course was gradually downward from this time on, and he died in June, 1921, of cardiac decompensation.

Comment.—The symptoms in this case of arterial hypertension were primarily cerebral, and later cardiac. During the period of cardiac embarrassment, there was an increase in albuminuria. At no time were nephritic symptoms predominant. The blood chemistry did not indicate retention.

CASE 4 (71).—*History.*—G., aged 74, seen first June 12, 1920, complained of dizzy spells and weakness.

Examination.—Some respiratory effort; marked arteriosclerosis. The left border of the heart was 4 cm. to left of the midclavicular line, in the sixth space, with showers of small râles at bases posteriorly. The urine showed 0.2 per cent. albumin, with many fine granular and rare cellular casts. Blood pressure, 185/105.

Course.—He made marked improvement on rest and digitalis, so that, within a month, the albumin decreased to a very faint trace. There were only a few fine granular casts. Blood chemistry, June 14: urea, 13.5; uric acid, 2.5; creatinin, 1.33; sugar, 0.083.

CASE 5 (6).—*History.*—J., aged 59, seen first May 12, 1920, had slight dyspnea on effort, flatulence, some mental confusion and amnesia.

Examination.—This revealed: Heart 2.5 cm. to left of midclavicular line, in fifth space; soft, blowing, systolic murmur at apex. No marked evidences of cardiac embarrassment. Arteriosclerosis moderate. Blood pressure, 240/125. May 12, blood showed: urea, 11; creatinin, 1.16; sugar, 0.09. Urine showed a trace of albumin and a few granular and hyaline casts.

Course.—At present, two years after first seen, he is up and about, showing progressive mental confusion.

CASE 6 (17).—*History.*—Mrs. K., seen first Aug. 31, 1916, aged 65, had had several fainting attacks, especially while straining at stool.

Examination.—Blood pressure, 280/150. Cerebral symptoms predominated, and increased gradually. The urine showed definite trace of albumin, and moderate casts, and the heart never gave any particular concern. In August, 1919, she had a partial aphasia, mental dulness and amnesia. Her blood pressure was then 225/138. Blood urea, 25.5; creatinin, 2 and sugar 0.142. The urine showed no increase in albumin and casts.

Course.—In January, 1920, she had lobular pneumonia when albumin and casts increased in the urine, and the heart became dilated. Blood chemistry at this time showed: uric acid, 2.37; creatinin, 1.17. The blood pressure was 240/135. Her heart gave no difficulty but she was more aphasic and amnesic. Blood urea was then 30.5; uric acid, 5.75; creatinin, 1.9 and sugar 0.11. The alkali reserve was 70.

The fundi, at no time, have shown hemorrhage.

Comment.—This patient has had predominating cerebral symptoms since 1914, is ambulatory, and has never, except during pneumonia, shown cardiac embarrassment or nephritic symptoms. The condition has been attributed to cerebral arteriosclerosis rather than to chronic uremia.

CASE 7 (21).—*History.*—J. L., was seen first April 19, 1914, aged 69, complaining of persistent headaches, and his physician had told him he had kidney trouble.

Examination.—He was then a sturdy appearing, well built man with ruddy face and a tendency to cyanosis. His blood pressure was 205/130. Heart borders slightly increased, and some crepitant râles at the bases of both lungs. Urine showed definite albumin, and many, fine, granular casts. He was mentally alert and normal. Peripheral arteries were moderately thickened.

Course.—Up to May, 1919, he was seen at intervals, and much improved, with albumin appearing in faint traces or absent. At that time, he had an acute cardiac breakdown with much albumin and many casts, gradually improving during the summer. In September, his blood urea was 27, creatinin 4 and sugar 10. To August, 1921, he gradually showed mental confusion, some amnesia, and general feebleness, though he was able to be up and about, and cardiac and nephritis symptoms were not prominent. He then had another cardiac breakdown following obstinate constipation. The blood showed high uric acid values in May and December, 1920, and August, 1921, and in September, 1919, creatinin was high (4 mg.), but in August, 1921, it had dropped to 1.9. All this time his diet had been practically constant and restricted.

Comment.—This man has been seen more or less regularly for eight years. His long continued hypertension has resulted in decreasing cardiac strength. On several occasions of heart decompensation, albumin and casts have appeared, disappearing with improved circulation. The kidneys have given no other cause of concern, though for nine months the urine has shown definite traces of albumin, and a few or moderate hyaline, granular or cellular casts.

CASE 8 (29).—*History.*—H., aged 51, was seen Sept. 28, 1919, complaining of shortness of breath and swelling of legs, for two months. Was passing less than a quart of urine daily. Digestion was normal. Recurring symptoms for one and one-half years.

Examination.—He showed moderate cyanosis and marked dyspnea, with heart dilated to anterior axillary line and regular; systolic murmur at apex. Blood pressure, 195/125. Urine: specific gravity, 1.012; albumin, 0.35 per cent.; many hyaline and granular casts, and few cellular casts. Blood urea, 13.5; creatinin, 0.08.

Course.—Under treatment the symptoms improved somewhat, though the heart remained dilated, and albumin and casts persisted. The edema decreased. October 21 the blood urea was 32.5; creatinin, 3.03, and sugar 0.0204. Urine showed more albumin (0.4 per cent.) and many hyaline, granular and cellular casts. He was then lost sight of, but died a few weeks later.

Comment.—This patient's symptoms were predominatingly cardiac, with obstinate renal embarrassment. The high sugar content of the blood is noteworthy though glycosuria did not appear.

CASE 9 (85).—*History.*—H., aged 50, was a typical "cardionephritic."

Examination.—When admitted to the clinic his blood pressure was 195/120; orthopnea; slight edema; oliguria, and marked albuminuria were present, with heart dilated and decompensated. His course was steadily downward for six months, although for a time he improved under cardiac stimulation, rest and limited diet.

Course.—July 3, six months after he was first seen, he again presented himself, with marked edema, cyanosis, dilated heart with auricular fibrillation. His blood at that time showed: urea, 17.5; uric acid, 4.1; creatinin, 2; sugar, 0.11. The alkali reserve was 77. There was marked oliguria, excessive albumin and casts. July 10: urea was 15; uric acid, 3.25; creatinin, 1.5; sugar, 0.083. Alkali reserve was 65. He died of heart failure a few weeks later.

CASE 10 (36).—*History.*—G., aged 69, complained of dyspnea and orthopnea; considerable cough and flatulence.

Examination.—Blood pressure, 185/105. Arteriosclerosis was marked; the heart was dilated 5 cm. to the left of midclavicular line and showed auricular fibrillation. Urine contained albumin, 0.1 per cent. The blood showed: urea, 22; creatinin, 1.95; sugar 0.07.

Course.—In the next two weeks there was some improvement, but he died suddenly. Necropsy showed marked myocarditis.

CASE 11 (20).—*History.*—H., aged 69, when first seen was semicomatose. For two months he had headaches on awaking, but for one week past was weak and had severe headaches, anorexia, and vomited the day before.

Examination.—Blood pressure, 225/125; urine much decreased and showing excessive albumin (0.35 per cent.); many casts of all kinds.

Course.—That night he had three convulsions on the left side of the body, but, when seen the next day, was not paralyzed. Blood pressure had fallen to 160/118, with pulse regular but weaker and the heart moderately dilated. The blood, next day, showed extremely high values, as follows: Urea, 99; creatinin, 7.4; sugar, 0.96. He died that night.

Comment.—This was evidently a case of hypertension of some duration seen near the termination of the disease when cerebral symptoms predominated. The high blood values showed serious retention. His heart, when first seen was fairly compensating. The clinical picture then suggested cerebral edema or uremia.

Another case of cerebral edema simulating uremia or "cardionephritis" is the folowing:

TABLE 6.—Miscellaneous Group, Showing Normal Blood Values in Two Cases of Orthostatic Albuminuria, Marked Albuminuria in Cardiac Decompensation Which Cleared Up with Improved Circulation. The Very High Values in the Case of Bichlorid Poisoning Have Been Noted by Others

			Urine						Blood Pressure	Blood Chemistry						Test Diet Urine					
Case	Age	Diagnosis	Albumin	Casts	Blood	Oliguria	Edema	Uremia		Urea	Uric Acid	Creatinin	Sugar	Alkali Res.	Pu	D.	N.	Sp. Gr.	Cl	N	Remarks
67 S.	28	Syphilitic nephritis	0.4%	+++	..	+	+	..	140/ 95	12.5	1.88	1.9	0.10	..	39	1,125	135	N.	0.98	7.27	Nephritic symptoms disappeared after specific treatment
92 R.	18	Orthostatic albuminuria	++	++	..	..	..	..	120/ 80	12.5	2.5	1	0.10	78	55	N.	N.	N.	....	....	No symptoms
64 R.	30	Orthostatic albuminuria	++	++	..	..	..	..	120/ 84	10	1.25	2	0.08	..	60	N.	N.	N.	....	....	No symptoms
M.	23	Cardiac decompensation	0.6%	+++	..	+	+++	..	130/ 80	....	....	....	....	..	..	435	263	F.±	4.76	14	Symptoms disappeared with cardiac improvement
83 McD.	28	Bichlorid poisoning	..	..	..	AN	..	+++	150/ 90	11.0	7.5	8	0.17	..	..	.....	. .	....	....	....	Anuria 48 hours; died
41 S.	12	Uremia	++++	+++	+	+	++	+++	140/ 90	5.25	6.25	3.99	....	..	22	.. ..	...	....	....	....	
23 C.	45	Chronic parench. nephritis	+++	+++	++	++	+++	+	190/120	4.25	....	2.5	....	11	..	.. ..	..	....	....	....	Duration 15 years, relapses with purpura
S.	62	Acute focal nephritis	+	+	+	+	+	..	145/100	....	....	....	....	..	..	412	571	F.±	2.97	9.5	Pus in tonsils; fever

CASE 12.—*History.*—Man aged 52, admitted to county hospital with some mental confusion and complaining of shortness of breath, cough and bloody sputum, was taken sick the day before. He had had heart trouble for about five months, saying that he got it by trying to save someone from drowning. He had swelling of the ankles for four or five years. Difficult to get history because of mental confusion.

Examination.—Much edema of the face and legs. The pupils were equal and reacted normally to light and accommodation. The heart area was increased, being about 2 cm. outside the left nipple line. The heart was irregular in force and rhythm and there was pulse deficit. The first sound at the apex was replaced by a blowing murmur. On account of obesity the outline of the liver was not made out but there was also edema of the abdominal wall. Urine showed specific gravity, 1.014, albumin and hyaline and granular casts, two plus.

Course.—He became comatose, had involuntary urination and defecation, and died in two days. Patient was shown before a class of medical students and discussed as a possible case of cerebral edema rather than one of uremia. Blood chemistry the day before death showed: urea, 29; creatinin, 1.01.

Necropsy Findings.—"Besides general edema there is an early gangrene of the toes of the right foot. The tips of the fingers are cyanotic and the hands are edematous. Two or three liters of amber colored fluid were found in the

TABLE 7.—URINE FINDINGS IN CASE 13

Day Urine	Albumin	Specific Gravity
On arising	0	1.028
11 a. m.	Def. trace	1.014
1:30 a. m.	Def. trace	1.024
4 p. m.	Def. trace	1.014
6 p. m.	Def. trace	1.018
8 p. m.	Def. trace	1.022
10 p. m. (retired)	Trace	1.024
11:30 p. m.	0	1.020

peritoneal cavity. The bowel wall is watery. The lungs are markedly emphysematous in front, both pleural cavities contain about a liter or more of straw colored fluid. The pericardial sac is distended with amber fluid. In the right auricle, especially in the anterior wall and in the appendix there is a large grayish organizing antemortem clot which is adherent to the wall. There are vegetations on the mitral valve. Sclerosis of the vessels and of the heart are not marked. There is a large infarct in the posterior portion in the upper lobe. The grayish antemortem embolus causing this infarct is found plugging one of the branches of the pulmonary arteries and there are multiple smaller infarcts. The whole lung is markedly edematous and congested. The left lung also shows several small hemorrhagic infarcts. The kidneys are of average size; the surfaces made by sectioning disclosed an hyperemia but no other gross changes. There is a marked edema of the brain. The pia arachnoid is raised high above the convolutions. There is no scarring of the meninges. The vessels at the base of the brain are moderately sclerotic but there is no evidence of thrombosis or softening in any portion of the brain."

MISCELLANEOUS GROUP

CASE 13 (92).—*History.*—R., aged 18, case of orthostatic albuminuria (Table 6), who had been refused admission to Annapolis on account of albuminuria. Never ill, nor conscious that anything was wrong. Table 7 shows albumin present only in the day urine.

Course.—The albuminuria was uninfluenced by diet and exercise, and repeated examinations showed no albumin in the urine passed on arising. The two hour

test diet was normal. The phenolsulphonephthalein output was 55 per cent. in two hours. Blood chemistry showed: urea, 12.5; uric acid, 2.5; creatinin, 1; sugar, 0.10. Alkali reserve, 78. This patient was later admitted to Annapolis.

Case 14 (64).—*History.*—R., aged 30, printer, case of orthostatic albuminuria, never knew he had albumin until he failed to pass the physical examination for the army. Repeated examinations of the urine showed trace of albumin and a few granular casts in spite of low protein diet, and not modified by exertion. Blood chemistry showed: urea, 10; uric acid, 1.25; creatinin, 2; sugar, 0.8. Two hour test practically normal. Phenolsulphonephthalein output, 60 per cent. Albumin was present only when patient was upright. In neither case was there any evidence of polycythemia as noted by F. Eichenberger.[28]

These two cases of albuminuria showed normal blood values and the effect of posture on the albuminuria. Ludwig Jehle,[29] in 1913, showed the effect of lordosis and kinking of the ureter in producing this phenomenon. Barker and Smith [30] reported six cases, finding that, if the patient stood in an exaggerated lordotic position for one half hour, albumin and casts appeared in the urine. Sonne catheterized the ureters in his patients, and found typical orthostatic albuminuria in the left kidney only, giving the explanation that the vertebrae compress the renal vein. More recently W. and S. L. Rieser,[31] show that the aorta, or mesenteric artery, acts as pincers of the left renal vein. These become operative when the aorta is projected forward by lordosis, or when the mesenteric artery is pulled to tautness by visceroptic tug from the mesocolon.

Case 15 (83).—McD., bichlorid poisoning; seen in coma. Had passed no urine for forty-eight hours. Blood showed extremely high values as follows: urea, 110; uric acid, 8; creatinin, 7.5; sugar, 0.17. Died within a few hours.

Case 16 (67).—S., aged 28; syphilitic nephritis; albumin, 4 per cent.; many casts. Phenolsulphonephthalein, 39 per cent.; blood showed: urea, 12.5; uric acid, 1.88; creatinin, 1.9; sugar, 0.1. The test diet was given with the following results:

Time	Volume, C.c.	Specific Gravity	Cl	N
8-10	165	1.010	0.29	0.6
10-12	330	1.008	1.056	0.729
12- 2	210	1.012	1	0.814
2- 4	150	1.016	1.2	0.726
4- 6	150	1.017	1.32	0.732
6- 9	120	1.016	1.10	0.75
Total day	1,125		0.70	0.727
Total night	135			

The albuminuria disappeared on specific treatment.

Case 17 (23).—C., aged 45; chronic parenchymatous nephritis; had had nephritis for eighteen years, with occasional relapses. Four years before had

28. Parkes Weber: Polycythemia, etc., New York, Paul Hoeber, 1922, p. 11.

29. An Explanation of Orthostatic Albuminuria, Editorial, J. A. M. A. **77**: 127 (July 9) 1921.

30. Barker, L. F., and Smith, J.: Functional Renal Tests in Orthostatic Albuminuria, Am. J. M. Sc. **141**:44, 1916.

31. Rieser, W., and S. L.: Etiology of Orthostatic Albuminuria, J. A. M. A. **78**:64 (March 4) 1922.

albuminuric retinitis. Blood pressure varied between 210 and 110. In July, 1918, was seen with anuria for forty-eight hours, and profuse purpura on the arms and legs, and marked hematuria. For six months she had been gradually failing; albuminuria had been excessive, there was marked edema, hydrothorax and ascites. Blood chemistry showed: urea, 42.5; uric acid, 2.5; sugar, 0.11. She was too sick to have a test diet, and died within a month.

Case 18.—S., aged 62; acute focal nephritis. This patient was seen during an attack of acute tonsillitis with fever. Her blood pressure was 125/100. Heart negative. Urine showed trace of albumin and few hyaline and granular casts, but ten days later, there was oliguria, some edema of ankles and lower eyelids, and the urine showed a definite trace of albumin, hyaline and granular casts and red corpuscles. There was no urinary calculus, and pyelitis and pyelonephrosis were ruled out. The test diet was as follows:

Time	Volume, C.c.	Specific Gravity	NaCl	N
8-10	37	1.009	....	....
10-12	75	1.014	....	....
12- 2	44	1.009	....	....
2- 4	61	1.014	....	....
4- 6	27	1.009	....	....
6- 8	168	1.005	....	....
Total day	412		2.97	9.5
Total night, 10/8	571			

Within a few weeks nephritic symptoms had all disappeared, and when seen three months later, she was entirely well.

Case 19.—Mrs. M., aged 23; cardiac decompensation; had been in bed for six weeks with cardiac decompensation. Left border of the heart 1½ inches to the left of midclavicular line, with mitral insufficiency and stenosis. The liver was four finger breadths below the costal margin, and tender, marked edema of ankles, face, eyelids and buttocks. Albumin, 0.6 per cent.; many hyaline and granular casts. The two hour test was as follows:

Time	Volume, C.c.	Specific Gravity	NaCl	N
8-10	39	1.012	....	....
10-12	59	1.012	....	....
12- 2	79	1.012	....	....
2- 4	76	1.016	....	....
4- 6	87.5	1.008	....	....
6- 8	94	1.012	....	....
Total day	345		4.76	14
Total night	263	1.011		

Case 20 (41).—S., aged 12; nephritis with edema; had been in bed for some time before, with edema for last seven weeks. Urea, 52.5; uric acid, 6.25; creatinin, 3.99; alkali reserve, 0.22. Patient died three weeks later.

CONCLUSIONS

1. Albuminuria as described may not be due to serious damage in the kidney and may even be excessive from extrarenal factors. Passive congestion of the kidneys occurs not only in cardiac breakdown due to valvular insufficiency but may be a result of long continued heart strain from arterial hypertension.

2. Albuminuria occurs so frequently as a part of the clinical picture of arterial hypertension that these cases form a large group in the

patients studied. While chronic interstitial nephritis is assumed to be present, the "renal crisis" is often due to myocardial weakness and results in passive renal congestion.

3. In a miscellaneous group, two cases of orthostatic or postural albuminuria are cited. Renal function tests show no marked disturbance in the kidneys.

4. But few cases of primary nephritis are recorded because not many were encountered.

5. Of the various functional tests, those using the urine are disappointing. The chemical examination of the blood seems to offer a means of early differentiation between renal or extrarenal albuminuria. The test diet for fixation of specific gravity, and for the estimation of chlorid and nitrogen excretion and water output also gives an early clue of renal function.

6. The term "cardionephritis" seems a misnomer in view of the fact that the nephritic symptoms may be largely due to congestion and not to extensive renal damage.

7. Efforts to make clinical and pathologic nephritis conform still fail because of the complicated mechanism of renal secretion.

8. Attention is called to the predominating symptoms in vascular hypertension. Sooner or later every patient shows singly or jointly (*a*) nephritis (*b*) cardiac or (*c*) cerebral symptoms.

CLINICAL EXPERIENCE WITH QUINIDIN *

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During the past year in this country and for some time previously abroad, there has been great interest in the restoration of normal mechanism by the action of quinidin sulphate in cases of auricular fibrillation. The present series of sixteen cases has been studied with special reference to the improvement in efficiency of the circulation following restoration of the normal rhythm, as judged by various subjective and objective criteria. Obviously, the fact that auricular fibrillation can be terminated is of little significance unless the health of the patient is thereby improved.

In general, the following routine of treatment was employed: The circulation was brought to the highest efficiency possible by rest, and in most cases by thorough digitalization. Two patients who had slow cardiac rates with no pulse deficit, cyanosis or edema, and whose only signs of cardiac insufficiency were dyspnea and limitation of activity, were not given digitalis. In the other cases, digitalis was stopped before the administration of quinidin. A small preliminary dose of quinidin sulphate was given to test for idiosyncrasy to the drug. No case of hypersensitivity was discovered. Then 2.0 gm. was administered daily in five doses of 0.4 gm. each at two hour intervals. This dosage was employed in order to maintain a high concentration in the body. It was continued until the cardiac mechanism became normal, or until unfavorable signs appeared, or until it became evident that the rhythm could not be changed. In one case 19 gm. of the drug was given. No untoward effects, except headache and an increase in the number of stools, were observed.

All observations on the mechanism were confirmed by electrocardiograms. The average systolic blood pressure during fibrillation was determined by the method of James and Hart.[1] The vital capacity is expressed in percentage of the normal, calculated according to the formula of West.[2]

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* From the Cardiographic Laboratory of the Johns Hopkins University and Hospital. Presented in abstract by title before the American Society for Clinical Investigation, Washington, D. C., May, 1922.

1. James, W. B., and Hart, T. S.: Am. J. M. Sc. **147**:63, 1914.

2. West, H. F.: Clinical Studies on Respiration; Comparison of Various Standards for Normal Vital Capacity of Lungs, Arch. Int. Med. **25**:306 (March) 1920.

CASE REPORTS

CASE 1.—*Arteriosclerosis. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 49. No history of acute rheumatic fever or syphilis. Scarlet fever at 12. Onset of cardiac symptoms four months before admission, with precordial pain and rapid development of palpitation, dyspnea and edema. On admission signs of congestive heart failure: cyanosis, orthopnea, edema. Large heart; no sign of valvular disease. Rhythm totally irregular. Pulse deficit from 10 to 12. Peripheral arteriosclerosis. Wassermann reaction negative. The signs of congestive heart failure disappeared with rest and thorough digitalization, but the patient remained unable to leave his bed without rapid reappearance of symptoms of cardiac failure.

CASE 2.—*Arteriosclerosis. Hypertension. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged 63. No satisfactory history of any acute infection. Onset of cardiac symptoms three years before admission with palpitation, dizziness, and edema of ankles. Symptoms slowly progressive with periods of relatively good health. On admission obesity, edema of ankles and of lung bases. Large heart. No evidence of valvular damage. Rhythm totally irregular. Pulse deficit 4. Peripheral arteriosclerosis. Wassermann reaction negative. Moderate improvement with rest in bed and digitalis.

CASE 3.—*Arteriosclerosis. Emphysema. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 77. No definite history of any acute infection. Patient noticed irregularity of pulse about three years before entrance. Anorexia and nausea only symptoms of cardiac insufficiency. On admission showed no dyspnea. Marked cyanosis. Slight edema of legs. Numerous râles at lung bases. Liver enlarged. Large heart. No sign of valvular disease. Rhythm totally irregular. No pulse deficit. Peripheral arteriosclerosis. Wassermann reaction negative. No digitalis given.

CASE 4.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged 48. Acute rheumatic fever at 34. Slight dyspnea for ten years. Nine months before entrance marked dyspnea and anorexia with great limitation of activity. Pulse irregular at that time. Digitalis for some time before admission without significant change. On admission slight cyanosis; many râles at lung bases. Heart large. Diastolic murmur at apex. Rhythm totally irregular. Pulse deficit 26. Liver enlarged. Wassermann reaction negative.

CASE 5.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged 38. Acute rheumatic fever at 8. Scarlet fever before 14. Onset of heart failure eighteen months before entrance, with dyspnea and nervousness. Shortly before entrance developed palpitation, precordial pain, edema and excessive fatigue. Digitalis did not relieve these symptoms. On admission showed slight cyanosis and râles at right lung base. Large heart. Mid-diastolic murmur at apex. Rhythm totally irregular. Pulse deficit 12.

CASE 6.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 58. Acute rheumatic fever at 43. Onset of cardiac symptoms two years before present entry with a transient attack of rapid irregular heart action, dyspnea, weakness and edema of ankles. Hospital history at that time records irregularity with pulse deficit of from 17 to 24. Constant administration of digitalis was necessary to enable him to carry on light work. On this admission slight cyanosis, slight dyspnea, no edema. Large heart. Apical systolic murmur; no diastolic heard. (Subsequently, after the onset of normal mechanism, a rough presystolic murmur was evident.) Rhythm totally irregular. No pulse deficit. Wassermann reaction negative.

CASE 7.—*Exophthalmic Goiter. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 58. Scarlet fever and tonsillitis in youth. Onset of symptoms of hyperthyroidism seven years before entrance. Four operations on

thyroid. Pulse totally irregular for one week following one of these. For six years patient had dyspnea and palpitation. For three weeks before entrance orthopnea and edema of ankles. On admission he showed recurrent thyroid enlargement, marked exophthalmos and tremor. Orthopnea. Cyanosis. Moderate general edema. Heart large. No sign of valvular disease. Rhythm totally irregular. Pulse deficit of 58. Wassermann reaction negative. Rapid rate and large deficit persisted despite rest and digitalization.

CASE 8.—*Arteriosclerosis. Emphysema. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 57. No satisfactory history of acute infections. Onset of cardiac symptoms two years before admission with dyspnea. Incapacitation for eight months. On admission dyspnea, cyanosis, edema. Emphysema. Peripheral arteriosclerosis. Large heart. No evidence of valvular disease. Rhythm totally irregular. No pulse deficit. Wassermann reaction negative. Slight improvement after rest and digitalis.

CASE 9.—*Rheumatic Heart Disease. Auricular Fibrillation. Myocardial Insufficiency (Slight).*—Male, aged 29. Periapical abscesses, tonsillitis and tonsillectomy one year before entrance. No acute rheumatic fever. Excessive fatigue. Slight dyspnea and indigestion for three years. On admission no dyspnea, cyanosis or edema. Heart slightly enlarged. First sound roughened. Rhythm totally irregular. Wassermann reaction negative. Digitalis not given. About ten weeks after discharge with normal rhythm the patient began to have palpitation and excessive fatigue again. His pulse was found to be totally irregular and he was readmitted in the same condition as on first entrance, for a second course of treatment.

CASE 10.—*Arteriosclerosis. Emphysema. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged 73. No satisfactory history of any acute infection. Onset of cardiac symptoms one year before admission with dyspnea, cough, edema. An electrocardiogram made four months before admission showed auricular fibrillation. On admission emphysema. Peripheral arteriosclerosis. Heart large. Systolic murmur at apex; diastolic at base. Rhythm totally irregular. No pulse deficit. Wassermann reaction negative. Rest and digitalis did not change the patient's condition.

CASE 11.—*Syphilis. Emphysema. Arteriosclerosis. Auricular Fibrillation. Myocardial Insufficiency. Hydrocele.*—Male, aged 58. Frequent tonsillitis in youth. Onset of cardiac symptoms with dyspnea ten years before entrance. Incapacitation for five years. On admission cyanosis, dyspnea, orthopnea, edema, obesity. Marked emphysema; heart large. No evidence of valvular disease. Rhythm totally irregular. No pulse deficit. Peripheral arteriosclerosis. Liver enlarged. Wassermann reaction positive. Gross signs of congestive heart failure disappeared with rest and digitalis.

CASE 12.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 60. No history of any acute infection. Symptoms of heart failure for fifteen years. Palpitation, dyspnea, anorexia, vomiting, edema. Two attacks of unconsciousness followed by aphasia. On admission marked dyspnea, râles at lung bases, large liver. Heart large. Diastolic murmur at apex. Rhythm totally irregular. Marked peripheral arteriosclerosis. Wassermann reaction negative. Deficit of from 6 to 10 persisted despite digitalization with reduction of heart rate to 65.

CASE 13.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged 54. Repeated tonsillitis in childhood. Onset of cardiac symptoms five years before entrance, with palpitation and shortness of breath. Three years before entrance rapid irregular heart action with increasing dyspnea. Intermittent progression of symptoms. On admission obesity, cyanosis, dyspnea. Râles at lung bases. Heart large. No murmurs. Rhythm totally irregular. Pulse deficit 30. Wassermann reaction negative. Moderate improvement followed rest and digitalis.

CASE 14.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Female, aged *22*. Repeated tonsillitis before 11. Admitted to hospital at 11 with tonsillitis, rheumatic heart disease, pericardial effusion, auricular fibrillation and signs of congestive heart failure. The patient established a fair degree of cardiac reserve but was readmitted nine years later with marked failure, from which there was a good recovery. The patient has constantly taken digitalis. On admission she showed slight edema. Large heart. Diastolic apical murmur. Totally irregular rhythm. Pulse deficit 8. Wassermann reaction negative.

CASE 15.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged 45. No history of acute rheumatic fever or syphilis. Long history of ill health. Onset of cardiac symptoms (dyspnea, vertigo, frothy sputum) one year before present entry. Electrocardiogram at that time showed auricular fibrillation. On admission dyspnea and cyanosis, no edema. Large heart. Middiastolic murmur at apex. Rhythm totally irregular. Pulse deficit 10. Wassermann reaction negative. Constant administration of digitalis was necessary to prevent incapacitation. Withdrawal of digitalis during administration of quinidin was followed promptly by serious congestive heart failure.

CASE 16.—*Rheumatic Heart Disease. Mitral Disease with Stenosis. Auricular Fibrillation. Myocardial Insufficiency.*—Male, aged *39*. Repeated sore throat. Onset of cardiac symptoms two years before admission with syncope, dyspnea, and gastro-intestinal symptoms. Dyspnea grew slowly worse. On admission dyspnea at rest and cyanosis. Râles at lung bases. Heart large. Low pitched diastolic apical murmur. Rhythm totally irregular. No pulse deficit. The patient was still bedridden after rest and digitalis.

COMMENT

Table 1 summarizes the results of our observations. Examination of this table shows that of sixteen patients studied, fourteen (88 per cent.) responded to the administration of quinidin by reverting to the normal mechanism. The average amount of the drug given to produce this result was 3.26 gm., the limits of variation being 0.4 gm. and 10.0 gm. This means that rhythm in most cases became regular on the second day of treatment, while the longest time which elapsed during successful treatment was five days. Of the fourteen patients in whom rhythm became regular, normal rhythm has persisted in eight. Six patients have had a normal rhythm for six months or more. The eight patients in whom rhythm became presistently regular all showed a remarkable improvement, both subjective and objective, while none of the remaining six who soon reverted to auricular fibrillation showed improvement with the onset of normal mechanism. This observation is of great interest because it points strongly to a close correlation between the severity of myocardial damage and the persistence of auricular fibrillation. It is, however, noteworthy that there has been no close correlation between the degree of heart failure and the success of quinidin treatment.

Conclusions as to the relation of the various etiologic factors, the duration of cardiac symptoms, and the age of the patient, to the success

TABLE 1.—Summary of Observations

Case No.	Etiologic Factor	Duration of Cardiac Symptoms	Degree of Cardiac Failure	Quinidin		Rhythm After Quinidin	Duration of Normal Rhythm †	Subjective Condition	Vital Capacity, per Cent. of Normal		Systolic Blood Pressure	
				Days Given	Total Dosage, Gm.				Auricular Fibrillation, per Cent.	Normal Rhythm, per Cent.	Auricular Fibrillation, Average	Normal Rhythm
1	Arteriosclerosis.....	5 months	Third	2	1.6	Auricular fibrillation						
				3	5.6	Normal rhythm	9 months	Much improved	...	85	110	140
2	Arteriosclerosis, hypertension	3 years	Second	2	3.0	Normal rhythm	3 days	Not changed	58	...	184	220
				3	5.0	Normal rhythm	6 months	Improved	...	78		
3	Arteriosclerosis.....	3 years	First	4	6.4	Auricular flutter	.....	.....	52	...	108	
				1	0.8	Normal rhythm	6½ months	Much improved	...	66	...	141
4	Rheumatic infection....	10 years (fibrillation 9 months)	Second	4	8.0	Auricular fibrillation	.....	.....	36	...	80	
				3	6.0	Normal rhythm	6 months	Distinctly improved	...	47	...	120
5	Rheumatic infection....	18 months	Second	5	10.0	Normal rhythm	6 months	Greatly improved	50	87	92	120
6	Rheumatic infection....	1 year	First	½	0.8	Normal rhythm	6 months	Distinctly improved	67	92	95	105
7	Thyrotoxicosis.....	6 years	Third	1	1.6	Normal rhythm	25 days	Greatly improved	50	...	88	
				1	2.0	Normal rhythm	3½ months	Greatly improved	...	83	...	130
8	Arteriosclerosis.....	2 years	Third	4	7.0	Normal rhythm	3 months	Distinctly improved	48	63	100	110
9	Rheumatic infection....	3 years	None	1	1.1	Normal rhythm	7 days	Not changed	110	126	93	120
				1.5 hrs.	0.4	Normal rhythm	1 month	Not changed	126	128		
				1	1.6	Normal rhythm	2 months	Not changed	130	130	95	125
10	Arteriosclerosis.....	1 year	Second	1	1.0	Normal rhythm	2 days	Not changed	...	...	180	190
				3	3.0	Normal rhythm	3 days	Not changed				
				2	1.2	Normal rhythm	2 weeks	Not changed				
11	Arteriosclerosis, syphilis	10 years	Second	1	2.0	Normal rhythm	9 days	Improved	40	65	120	136
				9	18.0	Auricular fibrillation						
12	Rheumatic infection....	15 years	Third	2	2.8	Normal rhythm	2 days	Not changed	40	35	100	145
				7	10.8	Auricular fibrillation						
13	Rheumatic infection....	5 years (fibrillation 3 years)	Third	1	1.6	Normal rhythm	3 days	Not changed	...	...	....	152
				2	2.8	Normal rhythm	2 days					
14	Rheumatic infection....	11 years (fibrillation 11 years)	Second	3	6.0	Normal rhythm	24 hours	Not changed	48	...	120	
15	Rheumatic infection....	1 year	Third	5	10.0	Auricular fibrillation	.....	.....	44	...	90	
				2	4.0	Auricular fibrillation						
16	Rheumatic infection....	2 years	Third	7	13.0	Auricular fibrillation	.....	.....	40	...	106	
				9	19.0	Auricular fibrillation						

* Cardiac failure is described in the following terms: first degree: breathlessness on moderate exertion the chief symptom; second degree: breathlessness on slight exertion, râles at lung bases, edema at the end of the day, moderate limitation of the patient's activities; third degree: breathlessness at rest, gross edema, cyanosis, incapacitation.

† Normal rhythm has persisted to the time of writing with the exception of Cases 9, 10, 13 and 14, the last three of which resulted in death.

of the treatment are not warranted in a series so small. Of great interest, however, is the success with which a very severe and long-standing case of thyrotoxicosis was treated.

With regard to the criteria of improvement, in addition to the subjective improvement which was experienced by all patients who became persistently regular, we have noted that they have been able to live at a considerably higher level of activity than was possible previously. Moreover, there has been consistently a rise in the vital capacity and systolic blood pressure of these patients. Determinations by Dr. Harold J. Stewart [3] of the degree of oxygen saturation of the arterial and venous blood further demonstrated a circulatory improvement in most of these patients.

Table 2 is a compilation of the cases of auricular fibrillation treated with quinidin which are reported in the literature, of which the total is now over 600. Normal rhythm was restored in more than 50 per cent. of these patients. Reports of patients treated with quinin have not been included.

Accidents.—There was a fatal outcome during the hospital course in three of the cases in this series. Unfortunately, two of these deaths seem to be associated with the change in rhythm which followed the administration of quinidin.

Shortly after reverting to normal mechanism for the second time, the patient reported as Case 13 [3a] showed signs of renal insufficiency which were not previously present. Two days after the onset of normal mechanism she again relapsed to auricular fibrillation. The urine output fell almost to zero and examination of the blood showed increasing nitrogen retention. The patient had repeated convulsions and died five days after the onset of these symptoms. Necropsy revealed the presence of a friable thrombus in the left auricle. A large proportion of each kidney showed anemic infarction and surrounding hemorrhage. There was also infarction of the spleen and embolism of the abdominal aorta at its bifurcation. The brain showed a fresh clot over the right cerebral hemisphere. There was a moderate degree of mitral stenosis.

There was no change in the subjective condition of the patient reported as Case 14 after her pulse became regular. About twelve hours after the onset of normal mechanism she suddenly sat up and immediately thereafter fell out of bed and was found to be dead. No necropsy was permitted.

The patient reported as Case 11 was readmitted one month after her final assumption of normal rhythm. Three days previously symptoms suggestive of cerebral accident had suddenly occurred. Examina-

3. Stewart, H. J.: Arch. Int. Med. (to be published).

3a. This case is reported by the courtesy of Dr. Louis V. Hamman.

TABLE 2.—Compilation of Cases of Auricular Fibrillation Reported Treated with Quinidin

Authors	Number Treated	Reversions to Normal Rhythm
Arneil [4]	9	4
Arrillaga, Waldrop and Guglielmetti [5]	14	9
Benjamin and von Kapff [6]	27	18
Bock [7]	35	16
Boden and Neukirch [8]	17	6
Burwell and Dieuaide	16	14
Clere and Deschamps [9]	24	12
Drury and Iliescu [10]	13	6
Ellis and Clark-Kennedy [11]	7	5
Eyster and Fahr [12]	2	1
Faber [13]	2	1
Frey [14]	50	21
Fløystrup [15]	2	2
Haass [16]	44	27
Hamburger and Priest [17]	18	11
Hart [18]	15	5
Hewlett and Sweeney [19]	12	6
Jenny [20]	18	17
Klewitz [21]	13	1
Leschke and Ohm [22]	1	1
Levy [23]	25	11
Lian and Robin [24]	4	3
Oppenheimer, Mann and Felberbaum [25]	56	25
Romberg [26]	22	17
Sappington [27]	1	1
Schott [28]	2	2
Smith [29]	12	6
Van Tilburg [30]	10	8
Von Bergman [31]	9	6
White, Marvin and Viko [32]	75	51
Wilson and Herrmann [33]	1	1
Wisser [34]	11	4
Wolferth [35]	12	7
Wybauw, Dumont and Joos [36]	27	14
Total	606	339 (55.9%)

4. Arneil, P.: Hygiea **83**: 529, 1921.
5. Arrillaga, F. C.; Waldrop, C. P., and Guglielmetti, J.: Prensa med. Argentina, **8**, 1922, (abstr. in Presse méd. **30**: 352, 1922).
6. Benjamin and von Kapff, W.: Deutsch. med. Wchnschr. **47**: 10, 1921.
7. Bock, G.: Med. Klin. **17**: 1052, 1921.
8. Boden, E., and Neukirch, P.: Deutsch. Arch. f. klin. Med. **136**: 181, 1921.
9. Clere, A., and Deschamps, N.: Presse méd. **30**: 305, 1922.
10. Drury, A. N., and Iliescu, C. C.: Brit. M. J. **2**: 511, 1921.
11. Ellis, A. W. M., and Clark-Kennedy, A. E.: Lancet **2**: 894, 1921.
12. Eyster, J. A. E., and Fahr, G. E.: Arch. Int. Med. **29**: 59, 1922.
13. Faber, K.: Ugeskr. f. Læger **83**: 577, 1921.
14. Frey, W.: Deutsch. Arch. f. klin. Med. **136**: 70, 1921.
15. Fløystrup, G.: Ugeskr. f. Læger **83**: 1380, 1921.
16. Haass, H.: Berl. klin. Wchnschr. **58**: 540, 1921
17. Hamburger, W. W., and Priest, W. S.: J. A. M. A. **79**: 187 (July 15) 1922.
18. Hart, T. S.: J. A. M. A. **79**: 69 (July 1) 1922.
19. Hewlett, A. W., and Sweeney, J. P.: J. A. M. A. **77**: 1793 (Dec. 3) 1921.
20. Jenny, E.: Schweiz. med. Wchnschr. **51**: 272, 1921
21. Klewitz, F.: Deutsch. med. Wchnschr. **46**: 8, 1920.
22. Leschke, E., and Ohm, R.: München. med. Wchnschr. **68**: 65, 1921.
23. Levy, R. L.: New York State J. M. **22**: 276, 1922.
24. Lian, C., and Robin, V.: Bull. et mém. Soc. méd. de hôp. de Par. **46**: 23, 1922.
25. Oppenheimer, B. S., Mann, H., and Felberbaum, D.: J. A. M. A. **78**: 1732 (June 3) 1922.
26. Romberg, E.: Krankheiten des Herzens, Ed. 2, Munich, 1921.
27. Sappington, S. W.: J. A. M. A. **78**: 59 (Jan. 7) 1922.
28. Schott, E.: Deutsch. Arch. f. klin. Med. **134**: 208, 1920.
29. Smith, F. M.: J. A. M. A. **78**: 877 (March 25) 1922.
30. Van Tilburg, J.: Nederl. Tijdschr. v. Geneesk. **2**: 1555, 1921.
31. Von Bergman, G.: München. med. Wchnschr. **66**: 705, 1919.
32. White, P. D., Marvin, H. M., and Viko, L. E.: J. A. M. A. **78**: 1839 (June 10) 1922.
33. Wilson, F. N., and Herrmann, G. R.: J. A. M. A. **78**: 865 (March 25) 1922.
34. Wisser: Inaug. Dissertation, Cologne, 1920.
35. Wolferth, C. C.: Am. J. M. Sc. **162**: 812, 1921.
36. Wybauw, R., Dumont and Joos: Policlinique (Brussels) March 1, 1921 (abstr. in Arch. d. mal du cœur **14**: 564, 1921).

tion showed increased reflexes on the right side and a right facial weakness. The pulse was totally irregular, with short periods of regularity. An attempt was made to control the auricular fibrillation by the administration of quinidin (two doses of 0.2 gm. each). This was ineffectual. The patient became comatose and shortly thereafter died. At necropsy it was found that there was a thrombus in the left middle cerebral artery and an infarction of the spleen. There was a moderate degree of stenosis of the mitral valve but there was no thrombus within the heart. There was extensive arteriosclerosis.

The frequent occurrence of embolism in cases of longstanding auricular fibrillation is well known. Mackenzie [37] and Orr [38] suggested that the contractions of the auricle, after quinidin had caused a resumption of its normal activity, might serve to detach emboli from intra-auricular clots. Table 3 shows that fourteen accidents resembling embolism have been reported as following closely the onset of normal rhythm in

TABLE 3.—Accidents Suggesting Embolism Following the Onset of Normal Rhythm in Cases Treated with Quinidin

	Cases	Deaths
Benjamin and von Kapff [6]	1	1
Burwell and Dieuaide	2	2
Ellis and Clark-Kennedy [11]	2	2
Groedel [39]	1	1
Hewlett and Sweeney [16]	1	1
Levy [23]	2	1
Sappington [27]	1	1
White, Marvin and Viko [32]	3	2
Wilson and Herrmann [33]	1	0
Total	14	11

cases of auricular fibrillation treated with quinidin. Eleven of these accidents were fatal. Up to the present, however, no pathologic evidence as to the nature of these accidents has been available.

The necropsy findings in Case 13 leave no doubt that this patient's death was due to the mechanism suggested by Mackenzie and Orr. In Case 14 we can only speculate on the basis of the clinical course that the same mechanism was responsible for the patient's death. In Case 11 the hemiplegia occurred while the patient's pulse was totally irregular and, since there was no intra-auricular thrombus, it is felt that this fatality is not attributable to the use of quinidin.

The occurrence of such accidents in small series of cases brings out the fact that patients should be carefully studied before being given quinidin. It is, of course, impossible to decide whether or not there is present an intra-auricular thrombus. Therefore, the decision as to the

37. Mackenzie, J.: Brit. M. J. **2**:576, 1921.
38. Orr, J.: Brit. M. J. **2**:576, 1921.
39. Groedel, F. M.: Therap. d. Gegenw. **62**:172, 1921.

use of the drug in a given case must be based upon a consideration of the degree of the patient's incapacitation after the usual therapy has been employed and of the improvement to be expected from a restoration of the normal rhythm. It must be borne in mind that embolism may occur during the course of auricular fibrillation and hence that the interpretation of embolic accidents following quinidin therapy must include a study of their relation to the onset of normal auricular activity. It is important to note that the drug is not in itself responsible for the embolism and that there is nothing to be gained by modification of the dosage.

CONCLUSIONS

Our observations of the patients' activity, systolic blood pressure, vital capacity, and subjective condition show a consistent improvement in all patients whose cardiac rhythm became regular and remained so for some time. Therefore, in patients with auricular fibrillation who cannot be brought to a satisfactory degree of circulatory efficiency by the usual therapeutic measures, an attempt to cause reversion to normal mechanism by quinidin is justified by the hope that the patient's health will be improved thereby. It is well established that the change in rhythm can be effected in at least 50 per cent. of the cases.

Two grams of quinidin sulphate may be administered daily without the production of severe toxic symptoms, and such a dosage results in a higher percentage of successes than does a smaller dosage.

So far as is known at present, the danger associated with the use of this drug lies not in its direct effects but in embolism from an intra-auricular thrombus, following the onset of normal auricular activity.

SUMMARY

1. Of sixteen cases of auricular fibrillation treated with quinidin sulphate, fourteen (88 per cent.) reverted to normal mechanism.

2. Regular rhythm has persisted in eight of these patients; in six for more than six months.

3. In the cases remaining persistently regular there has been marked improvement in the patient's health.

4. Death occurred in three patients; in one, shown to be due to embolism from an intra-auricular thrombus.

MYCOTIC (BACTERIAL) ANEURYSMS OF INTRAVASCULAR ORIGIN *

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With the development of modern methods of clinical diagnosis and pathologic study, it has become universally recognized that arterial aneurysms, in the great majority of cases, particularly aneurysms involving the arch of the aorta, are due to syphilis. Other etiologic factors of clinical importance, although ranking far below syphilis, are bacterial or so-called mycotic infections of arteries, trauma (most frequently in connection with war wounds) and arteriosclerosis. Extremely rare causes are congenital defects of vessels, adhesions pulling the artery wall outward (traction aneurysms), vascular tumors and chemical erosion, such as may occur in the walls of gastric ulcer or carcinomas. In horses, a parasitic worm, the *Strongylus armatus*, has caused aneurysms involving most commonly the mesenteric artery.

Bacterial infections may invade the vessel wall either from the outside or from within. Those coming from without are usually due to the extension of infection to the vessel walls from neighboring or contiguous inflammatory foci, attacking, first, the adventitia and then spreading inward, producing disintegration of tissue until the vessel is weakened enough to yield. These aneurysms are found most often in tuberculous cavities, the walls of abscesses or other areas of inflammation. Rarely, the aorta or pulmonary artery may be involved, in which case the infection usually comes from bronchial lymph nodes. According to present day views, the aneurysms in periarteritis nodosa are also to be regarded as due to infection from without. Klotz,[1] who has recently studied this condition and reviewed the literature, believes that the organisms concerned are streptococci. The infection is thought to be spread along the periarterial lymphatics.

The types of aneurysms to which we wish to call attention are those in whose production bacterial infection from within the vascular apparatus plays a part. Infection may be brought to arteries in a variety of ways and other factors beside infection may also be of importance in giving rise to aneurysm. There is no satisfactory name to include all the types and distinguish them from the aneurysms caused by infection from without. Embolism is frequently a factor, and aneurysms in whose formation embolism plays a part were called by

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1. Klotz: J. M. Research **32**:1, 1917.

the older writers, before the importance of infection was understood, embolic aneurysms. It is better to reserve this name for aneurysms regarded as being due to embolism without infection, although we do not believe that in any of the cases reported as purely embolic aneurysms without infection the absence of infection has been clearly established.

The term "mycotic" was adopted by Osler [2] and Eppinger [3] to call attention to the importance of infection. Eppinger's designation "mycotic embolic" for the type of aneurysm described by him has persisted. Benda [4] suggested "metastatic mycotic" to include the cases in which bacteria are carried to the vessel wall through the blood stream but without the aid of emboli. The name proposed by Benda does not cover the aneurysms caused by direct implantation of infection on the aorta and pulmonary artery. We have, therefore, designated the entire group "mycotic aneurysms of intravascular origin" which, at least, has the merit of directing attention to the two features they have in common.[5]

Tufnell [6] is usually credited with being the first to recognize the importance of embolism in the production of aneurysms, although Virchow,[7] in 1847, six years before Tufnell's publication, not only furnished the proof that embolism occurs but noted that at the seat of embolism sharply delimited destruction of the inner and middle arterial coats may be found. In two cases, he found arterial dilatation and sac formation at the site of embolism.

Tufnell believed that the aneurysms were caused by pressure behind the embolus and developed there. Ponfick,[8] however, in 1873, showed that they occurred at the site of the embolus. He believed that the mechanical effect of the embolus being pushed against the vessel wall by the blood pressure behind it, injured the vessel and thus gave rise to aneurysm. In some emboli he found sharp calcareous spicules. Where the emboli were soft, he explained the damage to the artery wall as being due to the constant pressure of the embolus against it, a mechanism which he considered analogous to decubital necrosis.

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2. Osler: Brit. M. J. **1**:467, 1885.
3. Eppinger: Arch. f. klin. Chir. **35**: 1887.
4. Benda: Lubarsch-Ostertag Ergebnisse. **8**:196, 1901.
5. The term mycotic, although sanctioned by long usage in this connection, is not altogether without objection since a special group of infections have come to be called the mycoses. With the exception of one aneurysm of the pulmonary artery, regarded as due to the spread of actinomycosis to the vessel wall (Reiche: Quoted from Thorel, Lubarsch-Ostertag, Ergebnisse **14**: 666, 1910) there are, so far as we are aware, no reports of aneurysms caused by any of the special group of mycoses.
6. Tufnell: Dublin Quart. J. M. Sc. **15**:371, 1853.
7. Virchow: Virchows Arch. f. path. Anat. **1**:272, 1847.
8. Ponfick: Virchows Arch. f. path. Anat. **58**:528, 1873; **67**:384, 1876.

Goodhart,[9] who reported a number of cases of so-called embolic aneurysms in 1877, was the first to advance the hypothesis that infectious processes were concerned in their formation. In 1878, Buchwald [10] found bacteria in polypoid vegetations in a pulmonary aneurysm, but believed the aneurysm came first and the vegetations and bacteria later. Osler,[2] in 1885, reported the finding of five aneurysms of the aorta in a patient with malignant endocarditis. He believed that the endocarditis and the aneurysms were due to the same infection. Langton and Bowlby[11] found numerous bacteria in the walls of embolic aneurysms and concluded that the infection was derived from the heart valves.

Eppinger,[3] whose classic monograph appeared in 1887, has contributed most to our knowledge of this subject. He described minutely the arterial changes in various stages of what he called mycotic embolic aneurysms, and demonstrated that the infection was conveyed by bacteria laden emboli detached from the heart valves to the arterial wall, and that the formation of aneurysm was dependent on partial disintegration of the wall, particularly the internal elastic lamina. Eppinger believed that the infection was carried to the adventitia and set up inflammation there first, later spreading to the media and intima. Later investigators accept this as the course of events when tiny infected emboli enter the vasa vasorum and are held in the adventitia, but it is now generally believed, through the work of Unger [12] and others, that when emboli plug the lumen of an artery, inflammatory processes begin on the inner surface and spread outward.

Although Eppinger and others who followed him established the etiologic importance of infection in the formation of aneurysms, the view was not abandoned that the mechanical effect of embolus alone on an artery wall is able to cause aneurysm. Lecky,[13] Libman [14] and Reiche [15] within the past twenty years have reported cases which have been cited in support of this view. In Libman's case, bacteria were found in the heart valves, and in Reiche's case, while blood cultures were negative at the time the aneurysm developed, they had previously been positive. In Lecky's case, a purely embolic etiology for the aneurysm is strongly suggested, but the case report is too incomplete for the acceptance of this view without question.

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9. Goodhart: Tr. Path. Soc. Lond. **28**:107, 1877.
10. Buchwald: Deutsch. med. Wchnschr. **4**: Nos. 1, 2 and 3, 1878.
11. Langton and Bowlby: Med.-Chir. Tr. **70**:117, 1887.
12. Unger: Beitr. z. path. Anat. u. z. allg. Path. **51**:137, 1911.
13. Lecky: Brit. M. J. **2**:1127, 1906.
14. Libman: Proc. New York Path. Soc., N. S. **5-6**:88, 1905-1906.
15. Reiche: Quoted from Libman, Am. J. M. Sc. **144**:313, 1912.

The more recent literature has shown that in the great majority of acute and subacute aneurysms developed from within the vessels, the underlying infection is some form of bacterial endocarditis. In this group of infections, aneurysms not only of the arteries but also of the heart walls and valves are not uncommon. Horder,[16] in 150 cases, found twelve aneurysms of the valves, four of the ventricular wall, four of the interventricular septum and four arterial aneurysms. In the series of Schottmüller,[17] Lenhartz [18] and Billings,[19] forty-four cases in all, six were found to have arterial aneurysms. Libman [20] has reported a total of thirteen mycotic aneurysms in three cases during the active stage of bacterial endocarditis. Cotton mentions the finding of but one aneurysm in a series of fifty-five cases of bacterial endocarditis. Morawitz [21] goes so far as to state that the development of aneurysms in unusual situations may aid in the diagnosis of "endocarditis lenta."

The older writers frequently attributed these aneurysms to rheumatism. Koch [22] in 1851, was the first to report such a case. From the published data in his case, as well as in many cases reported later, it seems more likely that bacterial endocarditis was present rather than rheumatism. More recently, rheumatism has not so often been regarded as of direct etiologic importance. In view of the difficulty in some cases, even at the present time, of making a differential diagnosis between the two conditions, it is not surprising that some confusion should occur. The importance of rheumatism as an etiologic factor in aneurysm formation will be discussed later.

The development of aneurysms during the course of bacteremia without endocarditis is rare. Buhl,[23] in 1866, found dissecting aneurysms of the ductus botalli in infants with puerperal infection. He concluded that the destructive processes must have been brought through the blood stream. Scattered reports of aneurysm formation in various conditions, principally bone and lung infections, are found, but until Ruge's [24] report, in 1905, none had had adequate bacteriologic study. Ruge's patient had osteomyelitis, pyemia and a coronary artery aneurysm in which streptococci were found. Since that time several cases have been studied bacteriologically, and streptococci,

16. Horder: Quart. J. M. **2**:289, 1908.
17. Schottmüller: München. med. Wchnschr. **57**:617, 1910.
18. Lenhartz: Nothnagel's specielle Pathologie und Therapie **3**:380, 1904.
19. Billings: Arch. Int. Med. **4**:409 (Sept.) 1909.
20. Libman: Proc. New York Path. Soc., N. S. **5-6**:43, 1905-1906.
21. Morrwitz: München. med. Wchnschr. **68**:1478, 1921.
22. Koch: Inaugural-Dissertation, Erlangen, 1851.
23. Buhl: Quoted from Thoma: Deutsch. med. Wchnschr. **15**:309, 1889.
24. Ruge: Deutsch. Ztschr. f. Chir. **80**:150, 1905.

pneumococci or staphylococci were recovered from the aneurysms. The aorta and the hepatic artery are the vessels that have been involved most often.

REPORT OF CASES

MYCOTIC ANEURYSMS OF THE AORTA

CASE 1.—*History.*—A. C., housewife, aged 31, white, American, was admitted to the University Hospital May 20, 1920, complaining of weakness and shortness of breath. Ever since she could remember, she had had palpitation and breathlessness on exertion, and during her childhood, a physician stated that she had a weak heart. In September, 1919, she began to suffer from chills, fever, cough and weakness. In October, her joints began to swell and were slightly painful. By February, 1920, she was somewhat improved but then developed what was called influenza. She had anorexia, sore eyes, headache, cough and pains all over her body, sensations of chilliness and marked weakness. Soon her feet and legs began to swell and she became so short of breath that she could not lie down flat. There was also some cough with white frothy expectoration.

She had never had any joint affections except the mild attack in the beginning of her present illness and had never had chorea. She had had measles and chickenpox in childhood; at 6 years she had some illness the nature of which was not known, but there was swelling of the body and redness of the skin. She had typhoid fever at 16.

Her habits had been good, she lived in good surroundings and she had done her housework. Her husband and two children are living and well.

Physical Examination.—She was of about medium stature, with poor nutrition and musculature. The skin was pale but there were no eruptions, except some miliaria on the chest and abdomen. The breathing was accelerated, shallow and somewhat labored. The lips and oral mucous membranes were pale, the teeth unclean, there were many cavities and unextracted roots and the gums were retracted. The tongue was heavily coated. The chest showed poor expansion, somewhat less on the left side. There were signs of congestion and some fluid at both bases. The cardiac apex impulse was weak and diffuse. The percussion area of precordial dulness was enormously increased, extending 13 cm. to the left of the midsternal line and 11 cm. to the right. The substernal dulness was 8 cm. in the first interspace, 12 cm. in the second and 17 cm. in the third. There were vigorous visible and palpable pulsations in the second and third interspaces to the right of the sternum. Loud systolic and diastolic murmurs were heard over the aortic area, probably also a separate apical systolic murmur. There was an occasional extrasystole. The liver was markedly enlarged and there were signs of a small amount of fluid in the abdomen. The spleen could not be palpated. There was moderate edema of the back but none of the legs. There was marked clubbing of the fingers. The pulsations in the larger arteries were visible; a distinct capillary pulse was seen and the Traube and Durosiez signs were present. The blood pressure was 100 systolic. Eyeground examination showed only pulsation of the retinal vessels.

Laboratory Examination.—The examinations of the urine showed a specific gravity of from 1.012 to 1.014, persistent cloud of albumin, many hyaline and granular casts, a slight excess of leukocytes and a few erythrocytes. The hemoglobin was 40 per cent., the erythrocyte count 2,230,000, and the leukocyte count 11,300 with 75 per cent. of polymorphonuclears. The Wassermann test was negative. A blood culture was positive, showing *Streptococcus viridans.*

The report of the roentgen ray of the chest by Dr. H. K. Pancoast was as follows: "Large heart. Right side of shadow less dense suggesting fluid on the right side May be fluid in the pericardial sac."

The temperature was of an irregular septic type, ranging from 97.4 to 103.6 F. Pericardial frictions developed and were heard over a wide area. There was manifest very little change in her general condition until June 5 when the pulse became very rapid and weak and the breathing labored. In a short time, death occurred.

Diagnosis.—Streptococcus viridans endocarditis; aortic and mitral regurgitation; myocarditis; pericarditis; cardiac decompensation with passive congestion of the lungs, liver and kidneys; mycotic aneurysm of the ascending arch of the aorta; subacute nephritis; secondary anemia.

Comment.—In spite of the fact that the literature affords no instances of a clinical diagnosis of mycotic aneurysm of the arch of the aorta confirmed at necropsy, the diagnosis in this case was based on the extraordinary degree and extent of visible and palpable pulsation to the right of the sternum in the second and third interspaces, associated with clear evidences of an aortic valve lesion, fever, leukocytosis and other evidences of an active infectious process. The discovery of pulsation over the arch of the aorta to the right of the sternum is to be expected in some cases of aortic regurgitation and is explained by the dilatation of the root of the aorta which occurs to a greater or less extent in many cases of this condition. The violence and the extent of the pulsation in this case were, however, so marked, and the evidence of unusual dilatation of the arch of the aorta on percussion so definite, that it seemed altogether probable that a distinctly pathologic dilatation (as contrasted with mere overdistention from stretching) existed in this case. The evident intravascular infection furnished a probable explanation, as acute (mycotic) aneurysmal dilatations are known to occur in association with infective endocarditis.

Pathologic Examination.—The necropsy was performed by Dr. M. T. McCutcheon. The following notes have been abstracted from his report:

The heart weighed 770 gm.; the epicardium was reddened and covered with fibrin which was easily stripped off in some places and adherent in others. The muscle was flaccid and of a turbid flesh color. The left side of the heart was greatly dilated; the right less so. The mural endocardium was generally transparent, but on the wall of the left ventricle below the aortic valve and on the left auricle above the mitral valve were found numerous soft verrucae. Two aortic leaflets show thickening, the right posterior one was much eroded and from it hung a soft vegetation about 8 mm. in length. The mitral valve was unthickened, but covered with many verrucae, some of which were quite pale and firm, while others appeared fresh. Smears made from the aorta just above the aortic valves and stained for bacteria showed streptococci.

In Figure 1 are shown an aneurysm and ulcerations in the ascending arch of the aorta and their relations to the aortic valve. Just above the right posterior sinus of Valsalva are two ragged ulcerated areas. On the corresponding aortic leaflet, there are two long but soft vegetations the tips of which could be inserted into the ulcerations. There are also some small vegetations about the ulcerations. In this area, about 2 cm. wide and 1 cm. long, the aortic wall is slightly thickened and pouched out. To the right, the diseased area narrows to an isthmus of thickened and slightly depressed vessel wall which connects it with a definite aneurysm above the anterior sinus of Valsalva. The aneurysm is irregularly rounded, approximately 2 cm. in diameter, and in the hardened specimen the floor is about 1.25 cm. below the surface of the adjacent part of the vessel. It extends just low enough to include and hide the exit of the right coronary artery. By probing back

through the artery, the exit was found not to be blocked but it was surrounded by fine vegetations. The wall of the aneurysm in places was from two to three times the thickness of the nearby vessel wall and was quite firm. There were folds in it suggesting that it had been larger during life and had contracted postmortem. For the most part it was covered by a smooth lining continuous with the intima and resembling it somewhat, although it was not quite so glistening and delicate. A few ragged vegetations were found growing out from this layer and on the left border of the aneurysm there was a ragged irregular area of ulceration about 6 mm. in diameter. At the edges

Fig. 1.—Case 1. Drawing of wall of left ventricle, aortic valves and the aorta just above the valves. There are two long ragged vegetations on the right posterior aortic leaflet. Above each on the inner surface of the aorta is an ulceration (*u*) to which the free end of the corresponding vegetation extends. The aneurysm (*a*) is above the anterior leaflet. The mouth of the right coronary artery at the lower end of the aneurysm is concealed but the vessel is patulous.

of the aneurysm the transition to healthy appearing aortic wall was abrupt. The rest of the aorta grossly appeared quite normal, except for one small subintimal yellow area 2.5 cm. above and to the left of the aneurysm.

A section taken at the edge of the aneurysm running from the normal aortic wall into the ulcerated infiltrated area showed the following: Where

the vessel wall is grossly unchanged, the intimal surface is largely missing, but what is present seems thickened. The internal elastic lamina is fairly solid. The media is irregularly degenerated, the muscle fibers in places being replaced by deep eosin staining spots and strands, at which places the elastica is also absent. Deep in the media, round cells begin to increase. The adventitia is very wide and consists of highly vascular, irregularly placed, strands of poorly stained connective tissue with a little muscle. Many of the vessels have a mantle of round cells. Some show distinct intimal swelling and one obliterated vessel is seen. There are a few round cell groups aside from the perivascular ones. The transition from the better preserved aorta to the aneurysmal part is indicated by a loose fibrous tissue participated in by the intima and media. Elastic tissue of the former practically disappears or becomes granular only, and of the latter is only fragmentary. The adventitia at this point is similar to that in the area previously described but somewhat more cellular, the elements being lymphoid and plasma cells. A few polymorphonuclear cells were seen. The blood vessels have distinctly more cellular walls. At the aneurysmal end of the section is an atheromatous abscess around the walls of which are polymorphonuclear cells, a few swollen cells of the endothelial type, some with phagocytic properties, and detritus. No bacteria were found in the sections stained for that purpose.

Comment.—It is apparent from the pathologic examination of the aneurysm that the inflammatory process involving the aorta must have been present for some time, a matter of at least months. In places the inflammatory reaction had almost completely subsided and the normal structure of the artery had been replaced by fibrous tissue. On account of the duration of the condition, the pathogenesis of the aneurysm is obscured. One of two modes of infection of the arterial wall seems probable. The infection may have been directly transferred to the inner surface of the aorta from the large ragged vegetations on the aortic valves which must constantly have come in contact with it. This view is favored by the finding of two acutely ulcerated areas in the aorta corresponding to the position in which the tips of two long vegetations would likely be thrown at each systole of the ventricle. On the other hand, a mycotic embolic infection through a coronary twig supplying the aorta cannot be excluded, and in view of the close proximity of the infective material to the exit of the coronary arteries, has just as much to support it as infection of the artery by contiguity.

Case 2.—*History.*—J. B., negro, male, aged 49, was admitted to the University Hospital, Nov. 4, 1921, complaining of aches and pains all over his body. He stated that about two years before admission he began to suffer from attacks of dizziness, and a year later he began to feel constantly tired and drowsy and had pains in his neck, chest, back and left leg. These symptoms persisted, and in addition, about six months ago, he noticed dyspnea on exertion. Four months ago, he had to give up work. Recently he thinks he "caught cold" and feels much worse since then. He has lost about 30 pounds.

He had gonorrhea at 18, and two severe and several mild attacks of rheumatism, the first attack at 20. Three years ago he had a hard pimple on the penis which disappeared in five days. He is a restaurant waiter and his meals are irregular. He has not used tobacco or alcohol excessively. He is married, his wife is living and well and has had one healthy child but no miscarriages.

Physical Examination.—He was a well nourished negro who did not appear as old as his stated age of 49. The oral mucous membrane was pale, the breath fetid and the tongue coated. There was moderate pyorrhea and several broken tooth crowns. The tonsils were large, congested and cryptic. The chest was somewhat barrel-shaped but the lungs were clear throughout. The heart was enlarged, principally to the left. By percussion, the left base was 13 cm. and the right base 4 cm. from the sternal line. The supracardiac dulness measured 6 cm. in the first interspace and 8 cm. in the second. The apex impulse was diffuse and its outer border was in the fifth interspace just outside the midclavicular line. No pulsations over the base were noted. There were no thrills. There were systolic and diastolic murmurs over the aortic area. An occasional extrasystole was heard. The pulse was of the collapsing type. Traube and Durosiez signs and a capillary pulse were present. The blood pressure was 125 systolic. Examination of the abdomen was negative, and neither spleen nor liver were palpable. The left knee was tender and swollen from effusion about the joint. Motion caused some pain.

After his admission to the hospital, the patient became more comfortable and in a few days the effusion in the knee subsided but did not disappear altogether. The temperature was irregular, varying beween 97 and 103 F., and did not fall with the improvement in the knee joint. The pulse range was from 90 to 120.

Laboratory Examination.—The urine examinations showed traces of albumin, hyaline, light and dark granular casts, a slight excess of leukocytes and on some examinations a few erythrocytes. The first blood count showed 3,600,000 erythrocytes, 5,600 leukocytes and 66 per cent. hemoglobin. The differential count was normal. The Wassermann test was negative. Two blood cultures were positive for a short chain nonhemolytic streptococcus. The phenolsulphonephthalein excretion was 40 per cent. in two hours, and the blood urea nitrogen was 19 mg. per 100 c.c.

Diagnosis.—A diagnosis of subacute infective (streptococcic) endocarditis was made.

Course.—November 16, there developed within the course of a few hours, complete left sided hemiplegia. The next day there were symptoms of meningitis, and a spinal puncture was done. The fluid was under great pressure and slightly cloudy. There were a great many leukocytes in the fluid and a streptococcus was grown resembling the one found in the blood culture. After a few days, the meningeal symptoms disappeared, but the hemiplegia remained. These phenomena were regarded as due to the lodgment in the brain of a septic embolus from the heart.

Symptoms of cardiac failure and passive congestion developed gradually and death occurred Jan. 4, 1922.

Necropsy Report.—The necropsy was performed by Dr. Baldwin Lucke to whom we are indebted for the pathologic report and the photographs of specimens.

Gross Anatomic Diagnosis: Aorta: Arteriosclerosis; early mycotic aneurysm. Heart: Hypertrophy; cloudy swelling; acute ulcerative and vegetative aortic and mitral endocarditis; slight coronary sclerosis. Lungs: Chronic passive congestion with superimposed edema and terminal congestion. Spleen: Septic infarction; acute diffuse splenitis. Kidneys: Chronic tubular nephritis; slight arteriosclerosis; infarction; slight hydronephrosis of left kidney.

Detailed Inspection of Heart and Aorta: The heart is greatly enlarged, somewhat globular in shape, and measures 14 by 12.5 cm.; weight, 550 gm. The epicardium is smooth and glistening and contains a normal amount of fat. The muscle is very dull, turbid and grayish brown. The left ventricular wall averages 20 mm. and the right 3 mm. in thickness. The papillary muscles are normal. The aortic leaflets are the seat of large soft vegetations; the right posterior cusp is almost entirely destroyed; the other two cusps possess

eroded margins. The mitral leaflets at their bases and midway between the base and the edge are covered with a few soft vegetations, the largest being about the size of a pea. The vegetations also extend down the chordae tendineae. The pulmonary and tricuspid valves have normal leaflets. The coronary arteries are slightly sclerotic. The aorta has normal calibre but much diminished elasticity. There are numerous, slightly elevated, hyaline and atheromatous patches, but nowhere any puckering. The aortic branches are slightly stiffened and have a slightly corrugated intimal surface. About 1 cm. above the left posterior cusp there is an ulceration of the aorta. This has an oval shape and measures 15 by 10 mm. The margins are fairly smooth. The erosion affects the intima and the greater part of the media. The bed of the ulceration consists of somewhat uneven fibrous tissue, probably adventitia. No definite bulging has as yet occurred; at the most there is slight cupping.

Section Through Vegetation from Heart Valve: The vegetation is papilloma-like, consisting of almost homogeneous eosin staining blood material in which are everywhere sprinkled irregularly deep blue staining bacterial colonies (cocci).

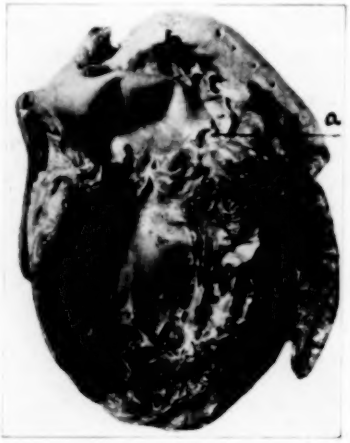

Fig. 2.—Case 2. The aneurysm (*a*), the surface of which measures 15 by 10 mm., is seen about 1 cm. above the left posterior leaflet.

Section Through Aneurysm of Aorta: There is an abrupt oval out-pouching, the walls of which consist of very much altered aortic tissue. On either side of the out-pouching, the aorta possesses a fairly normal intima with only here and there a slight hyaline thickening; the hyaline substance is sometimes broken up and contains large cells with fat droplets. The media is unchanged, except that around some of the vasa vasorum there are mantles of small round cells; groups of similar cells are scattered through out both media and adventitia, being particularly prominent in the latter. In addition, a few larger vessels in the adventitia possess irregularly thickened walls with hyaline plaques in the intima. At the edges of the out-pouching, the muscular and elastic fibers are suddenly curved outward and soon lost. At the base of the out-pouching there are small areas where much distorted remnants of elastic and muscular fibers can still be recognized. Generally, the wall of the dilatation consists of a much thinned out adventitia, which is composed of loosely arranged

fibrous tissue, between which are scattered groups of small round cells and occasional larger pigment containing phagocytes. The media is only represented by the traces of muscular and elastic fibers mentioned. There is an inner layer of newly formed tissue thrown into irregular folds and projections; it consists of very young connective tissue, the cells of which are stellate and embedded in a mucinoid ground substance. Internally, an endothelial lining covers this newly formed tissue, and is continuous with the endothelial lining of the more normal aorta. Bacterial stains failed to bring out any bacteria; stains for spirochetes were likewise unsuccessful.

Comment.—The aneurysm found in this patient's aorta was so small (Fig. 2) that clinical evidences of its presence could not be expected and none were discovered.

There were several unusual features of interest from the pathologist's viewpoint. In none of the cases previously reported has complete or virtually complete healing of an aortic mycotic aneurysm been observed. A number of cases have shown healing in part of the

Fig. 3.—Case 2. Low power magnification, photomicrograph of section of the entire length of the aneurysm, stained for elastic tissue. At the edges of the aneurysm the elastic fibers are suddenly curved outward and soon lost. At the base of the out-pouching small remnants of elastic and muscular fibers can still be recognized.

aneurysm, but at the same time, active inflammatory processes were going on in other parts. According to Dr. Lucke, the floor of the aneurysm in this case had been entirely covered over by a new growth of endothelium continuous with the endothelium lining the adjacent healthy portion of the vessel. No foci of acute inflammation were found anywhere. The destructive processes involving the media and the intima were of the usual type. These two tunics had been destroyed practically completely and were replaced by the layer of young connective tissue and endothelium previously mentioned. As shown in Figure 3, the wall of the aneurysm was much thinner than that of the normal part of the aorta.

On account of the chronicity of the aneurysm (Dr. Lucke estimated its age at six weeks at the very least), and the fact that the inflammatory processes had subsided, there was not much evidence on which to determine the route by which infection had been brought to the artery. Infection by continuity from the aortic valve could be excluded as the vessel between the aortic valve and the aneurysm was not involved. There is little likelihood that the infection had been implanted directly from the valve on the aorta as there were no vegetations present at the time of necropsy anywhere nearly long enough to have reached the area of the aneurysm. It would seem most probable that a minute embolus had entered the coronary circulation from the diseased aortic valve and become blocked in one of vasa vasorum supplying the first portion of the aorta, initiating an inflammation that resulted in a true mycotic embolic aneurysm. Another possibility, although less likely, is that the process started as a metastatic infection of the inner surface of the aorta.

MYCOTIC ANEURYSMS IN BRANCHES OF THE SYSTEMIC ARTERIAL TREE

Two cases that fall in this group, both of which were somewhat unusual have been observed recently in the University Hospital.

CASE 3.—*History.*—A. W., male, white, unmarried, aged 44, was admitted to the University Hospital, Sept. 19, 1917. About three months previous to admission, he had begun to have chills, fever and sweats which recurred at irregular intervals. In August a tooth was extracted for root abscess and pus evacuated. Since then, there had been no more chills and the temperature, which had previously gone as high as 104.3 F., no longer exceeded 101 F.

Physical Examination.—The heart was found moderately enlarged, and there were blowing systolic murmurs at the apex and base. There were some râles at the right base posteriorly. The liver was enlarged and extended 6 cm. below the costal margin. The spleen was easily palpated on deep inspiration. There was slight tenderness along the course of the left femoral artery extending from Poupart's ligament halfway down the thigh. Small purpuric spots were noted in the skin. The blood pressure was 145/95.

Laboratory Examination.—The blood examinations showed a slight secondary type of anemia with from 4,100,000 to 4,220,000 erythrocytes and from 77 to 82 per cent. hemoglobin. The leukocyte count varied between 8,200 with 71 per cent. of polymorphonuclear cells, and 16,800 with 84 per cent. of polymorphonuclears. The urine showed small amounts of albumin and occasional casts and red cells. A blood culture remained sterile. Two examinations of the blood for malaria were negative.

Course.—There was no change noted in his condition until September 29, when he complained of severe pain in the left groin. Slight swelling was noted in this area along the course of the femoral vessels. Moderate but irregular temperature, varying between 97 and 100.8 F., and a pulse range between 95 and 115 continued as before. The pain was very severe for a few days and then improved but persisted in lesser severity for a month or more. October 20, a distinctly localized tumor about the size of a walnut and with expansile pulsation was noted just below the left Poupart's ligament in the region that had previously been tender and swollen. The mass remained about the same size for a week or two but then began to grow smaller and the pulsations less marked.

The patient left the hospital on November 2 without any improvement in his general condition, but the pulsating mass continued to decrease in size and finally disappeared altogether. He died about a month later of gradually increasing toxemia and heart failure.

Comment.—In spite of the one negative blood culture, the diagnosis of subacute infective endocarditis seemed clear in this patient, based on the presence of chills, sweats, the persistence of irregular fever, cardiac enlargement and murmurs, enlargement of the spleen, embolic phenomena in the skin and kidneys and progressiveness of the condition eventuating in death.

The course of events leading up to the formation of the aneurysm was somewhat out of the ordinary. There was no evidence of arterial plugging by an embolus nor disturbance of circulation in the leg. At first the condition was thought to be a femoral phlebitis but later the signs of aneurysm became unmistakable. The most unusual feature was the rapid subsidence and eventual disappearance of clinical evidences of the aneurysm.

The occurrence of the aneurysm during the course of a subacute infective endocarditis, its rapid development and short course are in favor of the nature of the process being mycotic; there is no other reasonable explanation for it. Its situation near the point where the profunda femoris is given off would suggest that an embolus might have been lodged there, but in the absence of definite signs of embolism the question cannot be decided.

Case 4.—*History.*—E. R., white, male, aged 18, was admitted to the University Hospital Sept. 10, 1921, complaining of weakness, swelling of the legs and abdomen and palpitation of the heart. At the age of 5, he had a severe attack of acute rheumatic fever that kept him in bed for several months. He was then well until 8, when he had an illness said to be heart trouble with high fever. From this time on, he was never strong and always had palpitation of the heart on exertion. In 1916, he began having attacks of decompensation but recovered fairly well between attacks. The present illness began in April, 1921, and although he has had periods of some improvement, the tendency has been downward. He is very weak and short of breath, his abdomen and legs have become greatly swollen and he suffers from palpitation.

The patient is a Russian Jew and came to this country in 1912. Up to the present attack he had attended school, except during his periods of decompensation.

Physical Examination.—The boy had a fairly well developed frame but poor musculature. He was distinctly orthopneic. The skin was yellowish and muddy but there was no discoloration of the sclerae. There was generalized edema, involving the legs and flanks particularly. The left arm below the elbow was greatly swollen, owing to thrombosis in the axillary vein. The heart was tremendously enlarged, extending by percussion 6 cm. to the right of the midline, while the apex impulse was felt in the left midaxilla. The supracardiac dulness was 9 cm. in the first interspace and 11 cm. in the second. In the second left interspace there was an impulse systolic in time. There was a short systolic murmur at the apex and a markedly accentuated pulmonic second sound. The cardiac action was rapid, usually totally irregular, but with

occasional short periods of rapid regular rhythm. There were moist râles at the bases of both lungs, the liver was markedly enlarged and signs of a moderate degree of ascites were present. The blood pressure was 110/75.

Coming from behind the right sternoclavicular joint and extending upward and outward about 3 cm., there was a mass approximately 2 cm. in diameter, apparently just underneath the skin. Over it was seen and felt a violent expansile pulsation, systolic in time. The mass was not tender, the skin was freely movable over it and there was no evidence of inflammation. It could be collapsed by pressure. It divided into two branches, one of which extended outward and the other up into the neck. The pulse in the right brachial and radial arteries was weak but could not be compared with that of the left side on account of the venous thrombosis and great swelling of the left arm.

Laboratory Examination.—The blood examination showed 5,500,000 erythrocytes, 12,900 leukocytes and 96 per cent. hemoglobin. The differential count was normal. The Wassermann reaction was negative. The urine contained a cloud of albumin and many casts, the phenolsulphonephthalein excretion was 25 per cent. in two hours and the blood urea nitrogen was 60 mg. per 100 c.c. The blood culture remained sterile. Roentgen-ray examination of the chest showed a tremendously enlarged heart but no evidence of aneurysm either of the aorta or the pulmonary artery. Electrocardiograms showed auricular fibrillation with occasional short periods of regular ventricular tachycardia. Pulse tracings made simultaneously over the pulsating mass and the right radial artery showed the upstroke of the pulse wave in the latter approximately 0.25 second later than that obtained over the mass.

Course.—The patient remained in the hospital ten days. He was given large doses of digitalis with only slight improvement in his condition. At no time was there any elevation of temperature or clinical evidence of active infection. There was no change noted in the mass in his neck. It gave no symptoms and he had not been aware of its presence.

Diagnosis.—Chronic myocardial disease, probably mitral valvular disease of rheumatic origin; severe cardiac decompensation with passive congestion and edema; auricular fibrillation and paroxysmal ventricular tachycardia; chronic glomerular nephritis; aneurysm of the outer end of the innominate artery.

It was reported to us by the patient's physician, Dr. J. M. Prince, that he died of heart failure ten days after leaving the hospital.

Comment.—The point of particular interest in connection with the aneurysm observed in this patient is the question of etiology. Aneurysms of any description in patients under 20 are extremely rare. Le Boutillier,[25] in 1903, was able to collect only sixty cases. Most aneurysms in the young are either mycotic or due to congenital syphilis. Syphilis did not appear to be a factor in this patient. There were no clinical evidences of the disease and the Wassermann reaction, as stated, was negative. On account of the lack of history of the time of development of the aneurysm, such possibilities as a congenital or traumatic etiology cannot be ruled out altogether. Both, however, are beyond the bounds of probability. On the other hand, the history of severe rheumatism, also an obscure attack of fever with cardiac involvement, the extensive heart disease, the location of the aneurysm at a bifurcation of an artery and the lack of evidence of arterial

25. Le Boutillier: Am. J. M. Sc. **125**:778, 1903.

disease elsewhere, suggest strongly that the aneurysm owed its origin to an infected embolus from the heart and for this reason is included in the series of cases here reported.

DISCUSSION

Incidence and Distribution.—We have collected from the literature all the cases we could find that appear to fall in the group under discussion. Including the four cases reported in this paper, we were able to gather 217 cases. The aneurysms regarded by the older writers as embolic are included, since in most of them, the case reports show clearly that they were really mycotic-embolic. The few cases in which a diagnosis of rheumatic aneurysm of a peripheral artery seem justified are included in spite of the fact that the nature of the rheumatic virus is not established, since their clinical manifestations were similar to those of mycotic embolic aneurysms. The clinical reports of rheumatic aneurysms of the arch of the aorta have been excluded for reasons that will be discussed later.

Arteries in all parts of the body and of various sizes, from the very largest to tiny unnamed vessels (the latter particularly in the brain), may be the seat of mycotic aneurysms. Eppinger has called attention to their multiplicity, stating that it is one of the most constant features of the condition. In this group of 217 cases, more than one aneurysm was found in forty-nine. If complete necropsies had been made in all cases, doubtless many more would have been discovered. The various arteries and their unnamed branches were involved 264 times (Table 1) with a total of 382 plus "numerous aneurysms in three cases." In quite a number of cases, several or many branches of one artery exhibited aneurysms.

The artery most frequently involved is the aorta, sixty-six cases with a total of eighty-eight aneurysms having been found. The favorite site is the root and ascending arch. Next to the aorta, abdominal vessels, namely the superior mesenteric, the hepatic and splenic are attacked, and in these arteries mycotic infection is one of the most important causes of aneurysm. Intracranial aneurysms were found in only thirty-four cases, but the total number of aneurysms was high because of their multiplicity, particularly when small vessels were involved. The middle cerebral and its distribution, particularly the artery of the sylvian fissure was the most frequent situation of the intracranial aneurysms. The arms and legs were almost equally involved, the former in twenty-three and the latter in thirty-one cases. The aneurysms in the extremities were found most often in the large arteries, the femoral and brachial. They are rare in the pulmonary arteries as compared with the systemic, doubtless owing to the compara-

tive infrequency of right sided endocarditis. There were only six cases of aneurysm of the pulmonary artery and eight of its branches.

Etiology.—Mycotic aneurysms of intravascular origin always occur in association with some underlying infectious process, usually situated within the cardiovascular apparatus. Rarely, they follow blood stream infections from other sources. In this series of 217 cases, there was evidence of endocardial disease in 187, the remaining thirty cases occurring in connection with a variety of infections.

TABLE 1.—DISTRIBUTION OF MYCOTIC ANEURYSMS OF INTRAVASCULAR ORIGIN

Artery	Number of Cases	Total Number of Aneurysms
Aorta	66	88
Innominate	2	2
Vertebral	1	1
Basilar	4	4
Internal carotid	3	3
Anterior cerebral and main branches	3	3
Middle cerebral and main branches	14	23
Posterior cerebral	1	1
Posterior communicans	2	2
Small unspecified intracranial	14	49+ (Numerous in two cases)
Subclavian	1	1
Axillary	3	3
Brachial	10	10
Radial	5	5
Ulnar	5	5
Common iliac	7	7
External iliac	2	2
Internal iliac	1	2
Gluteal	3	3
Femoral	16	17
Profunda femoris	2	2
Popliteal	5	5
Posterior tibial	8	8
Coronary	9	22
Superior mesenteric and branches	24	38
Splenic and branches	15	15
Renal and branches	5	5
Hepatic and branches	19	19
Pulmonary	6	6
Pulmonary branches	8	31+ (Numerous in one case)
Total	264	382+ (Numerous in three cases)

The type of endocarditis usually found is what is commonly called subacute infective or bacterial endocarditis, the endocarditis lenta of Schottmüller, characterized by subacute or subchronic course, luxuriant vegetations on the heart valves, bacteremia and widespread embolism. The aneurysms also occur, but less commonly, in other types of endocarditis, varying from highly acute malignant forms of the disease to apparently quiescent lesions. The importance of true rheumatic endocarditis, except indirectly as it may offer a favorable site for the development of bacterial endocarditis, is undoubtedly small. In cases in which pathologic studies accompany the reports of aneurysms regarded as rheumatic, the findings have resembled more closely those of bacterial than those of rheumatic endocarditis.[26] In a few

26. Klotz: J. Path. & Bacteriol. **18**:259, 1913.

cases of peripheral aneurysms with embolic phenomena, the course and outcome seemed to justify the diagnosis of rheumatism as opposed to subacute infective endocarditis.

In the cases without endocarditis, lung and bone infections have been most often the source of the bacteremia. In ten cases there had been pneumonia, in three, septic lung infection, and in six, osteomyelitis. Other sources of infection were believed to be cystitis, gonorrheal rheumatism, infections of fingers and hands, phlegmonous angina, typhoid fever, influenza and anthrax.

The case for typhoid fever and anthrax is not proven. Four cases of supposed typhoid aneurysms have been reported, two of the aorta, one of the hepatic artery and one of the femoral. In the aortic cases, reported by Gils and Hecker,[27] neither the diagnoses of typhoid fever nor aneurysm could be regarded as substantiated from the evidence presented. In the other two cases reported by Quincke [28] and Cathcart,[29] the diagnosis of typhoid was not established. Oliver's case [30] was the only one believed to be due to anthrax, based on the finding of rods and spores resembling anthrax bacilli in sections of the aneurysm. No cultures were made, nor did the clinical picture and pathologic findings resemble those found in anthrax infections.

Influenzal infections in the form of an influenzal endocarditis may cause aneurysms, cases of this sort having been reported by Weinberger,[31] Horder [16] and Simons.[32] But whether or not the epidemic respiratory infection influenza ever causes aneurysm, is not so clear. Boinet [33] has insisted that it does, but no definite relationship between the infection and aneurysms is evident in the cases cited by him. Johnson [34] recently reported a case of aneurysm of the hepatic artery in a young man in whom symptoms of the aneurysm developed several months after the attack of influenza. This case, by no means conclusive, is the most suggestive thus far reported. It may be noted that the onset of subacute infective endocarditis not rarely suggests influenza and the later development of aneurysm might, therefore, readily be attributed to this infection. There is some evidence that influenza may

27. Gils: Arch. med. et de pharm. Militaires **22**:102, 1893. Hecker: Deutsch. Mil.-ärztl. Ztschr. **22**:1, 1893.

28. Quincke: Berl. klin. Wchnschr. **8**:349, 1871.

29. Cathcart: Southern M. J. **2**:593, 1909.

30. Oliver: Lancet **2**:1033, 1891.

31. Weinberger: Ztschr. f. klin. Med. **62**:456, 1907.

32. Simons: Quart. J. M. **7**:291, 1913.

33. Boinet: Nouveau Traitè de Medecine, Maladies des Artères et de l'Aorte **24**:169, 1913.

34. Johnson: Hospitalstid. **63**:860, 1920.

hasten the development of an aneurysm in an artery previously affected. Schelle [35] recorded a case in which rupture of an aneurysm of the descending aorta occurred during an attack of influenza. He believed the aneurysm had been present before the influenza, but that the rupture was due to the settling of the influenzal mycosis in the aneurysm. Huchard [36] observed rapid development of an aneurysm of the aorta in a patient with "gouty aortitis" during the course of an influenzal infection followed by pneumonia.

Malaria was formerly regarded as a cause of aneurysm but this view is no longer held. Possibly, the irregular fever of endocarditis may have occasioned the belief.

Age and Sex.—The age and sex of patients with mycotic aneurysms is determined by the age and sex incidence of the diseases giving rise to the aneurysms. The age was stated in 174 cases and is summarized by decades in Table 2. The youngest patient was 4 years old and the

TABLE 2.—AGE OF PATIENTS ARRANGED BY DECADES

Age	Number of Cases
1-10	14
11-20	50
21-30	57
31-40	32
41-50	14
51-60	5
61-70	1
71-80	1

oldest 78. Most cases occur during the second, third and fourth decades. This is in marked contrast to syphilitic aneurysms which are found most often in the fifth decade. The sex was stated in 178 cases, of which 121 were males and fifty-seven females.

Bacteriology.—In the cases with endocarditis, there has usually been little difficulty in demonstrating organisms in stained sections of the heart valves, and frequently they have also been found in the aneurysms. But apparently the arterial walls do not furnish so favorable a habitat for them as the heart valves for they tend to disappear from the aneurysms as the latter arrive at more chronic stages. Our Cases 1 and 2 illustrate the fact that organisms may be present in abundance, yet none are to be discovered in the aneurysms themselves.

The organisms most frequently recovered from blood cultures, cultures from the heart valves or from the aneurysms have been streptococci, mostly nonhemolytic types. Staphylococci and pneumococci have also been found a number of times. In at least three cases

35. Schelle: Inaugural-Dissertation, Würzburg, 1893.
36. Huchard: J. Pract., p. 579, 1896.

the influenza bacillus has been cultured and once the gonococcus. Various rod forms have been seen in sections but have not been cultured.

Pathogenesis.—Mycotic infection of arteries from within, leading to aneurysm formation may occur in the following ways: (1) by the lodgment of infected emboli in the lumina of vessels or in the vasa vasorum; (2) by the settling of bacteria on the inner surface of a vessel or in the vasa vasorum, and (3) by continuity or contiguity of infection from the aortic or pulmonic valves.

In the development of mycotic aneurysms beyond the aorta and the pulmonary artery, emboli usually play an important part. The size of the vessel involved depends on the size of the embolus. Rarely, one is large enough to be caught at the bifurcation of the aorta, and in Aitken's case [37] an infected embolus held there was believed to have given rise to an aneurysm. Eppinger has pointed out that mycotic embolic aneurysms are found in situations where emboli are most liable to lodge, namely, the bifurcations of arteries, places where the lumen rapidly narrows or where the vessel makes a sharp turn.

The part usually played by the embolus, so far as aneurysm formation is concerned, is that of bringing infection in contact with the vessel wall. The rôle was well demonstrated in a case reported by Pel [38] in which a soft riding embolus, partly in the femoral and partly in the profunda femoris but not obstructing either vessel, had given rise to beginning aneurysm of the femoral at the point where it lay in apposition to the wall of the artery.

Mechanical injury of vessel walls by emboli is rarely, if ever, more than a minor factor in the production of aneurysms. We have cited above the more recent cases regarded as of purely embolic origin and called attention to the inconclusiveness of the evidence in support of that view.

Aneurysms due to emboli carried through the vasa vasorum are usually found in the ascending arch of the aorta or nearby. Typical cases have been reported by Osler,[2] Eppinger,[3] and J. McCrae,[39] and others. The location of the aneurysms and the close proximity of aortic valve vegetations to the mouths of the coronary arteries in such cases suggests the view that tiny emboli are carried through the coronary arteries to the twigs supplying the region of the ascending arch.

Almost invariably, mycotic embolic aneurysms in the systemic arteries are associated with left sided endocarditis and in the pul-

37. Aitken: Brit. M. J. **1**:1655, 1898.

38. Pel: Ztschr. f. klin. Med. **12**:327, 1887.

39. McCrae: J. Path. & Bacteriol. **10**:373, 1904-1905.

monary arteries with right sided endocarditis. Entz,[40] however, reported a case of aneurysm of the pulmonary artery in which there was only mitral endocarditis. An embolus was believed to have been detached from the mitral valve, and to have traveled through a patulous ductus botalli to the pulmonary artery. Beatty and Hall [41] observed a case with an obscure septic infection, femoral venous thrombosis, and signs of pulmonary embolism. At the necropsy aneurysms were found in branches of the pulmonary artery and it was suggested that embolism had occurred from the venous thrombosis, although an organized thrombus was found in the right ventricle so that the direct source of the pulmonary embolism remained uncertain.

Direct infection of the inner surfaces of arteries by bacteria circulating in the blood stream is very rare. Uninjured intima is extremely resistant to infection. Clutton and Dudgeon,[42] Edenhuizen [43] and Merke,[44] in their cases of aneurysm, favored the view that infection of the artery had occurred in intimal defects due to preexisting arteriosclerosis. The aneurysms were situated in the midst of patches of arteriosclerosis. Merke found, in addition to aneurysms, verrucose deposits on calcified plaques. Ruge [45] was unable to decide in his case of coronary aneurysm whether infection had begun on the inner surface of the artery or in the vasa vasorum. Moriani [46] found plugs of diplococci within the vasa vasorum, and he believed that infection had arisen by that route in his case. Jordan [47] also believed that the infection, in the aneurysm of the aorta observed by him, had arisen through the vasa vasorum.

Aneurysms due to continuity or contiguity of infection from heart valves occur in the beginning portion of the aorta and the pulmonary artery. In these situations they are found more often than any other type of mycotic aneurysms. It is often impossible to tell which of the two has been responsible for the arterial involvement. Infection by continuity spreads from an aortic or pulmonary valve onto the vessel, producing first an endarteritis, and later, by penetration of infection to deeper layers, an aneurysm. Infection by contiguity is carried directly from the valve to the vessel by the slapping of the infected valve against the artery wall. Trauma may aid in the transfer of

40. Entz: Pester med.-chir. Presse **47**:293, 1911.

41. Beatty and Hall: Proc. Roy. Soc. Med., London, Path. Section, p. 147, 1912.

42. Clutton and Dudgeon: Lancet **1**:556, 1908.

43. Edenhuizen: Frankfurter Ztschr. f. Path. **16**:150, 1914.

44. Merke: Schweiz. med. Wchnschr. **7**:122, 1920.

45. Ruge: Deutsch. Ztschr. f. Chir. **80**:150, 1905.

46. Moriani: Quoted from abstract in Centralbl. f. allg. Path. u. path. Anat. **21**:427, 1910.

47. Jordan: Lancet **1**:515, 1903.

infection. Libman [48] believes that the impact of a valve containing calcific material against the aorta, even in the absence of infection may cause a small aneurysm.

Whether or not aneurysm formation will occur following infection of an artery depends on the extent and degree of destructiveness of the inflammation. If it remains localized to the intima, there may be ulceration but no aneurysm. If it begins in the deeper layers, there may be merely areas of necrosis or abscess formation. Yielding of the vessel is dependent on destruction of the elastic tissue, particularly the internal elastic lamina. If destruction of tissue is very rapid, perforation may occur before the vessel has had time to yield, and there may be free hemorrhage or the formation of a false aneurysm.

Infective lesions may occasionally be indirectly concerned in the formation of aneurysms. In cases reported by Gilewski,[49] and others, aneurysms of the pulmonary artery have followed a high grade mitral stenosis of rheumatic origin. Hart [50] reported an aneurysm of the right sinus of Valsalva with thin translucent walls. He regarded the aneurysm as due to the loss of elasticity in the valve which was the seat of an old inflammation. Kraus [51] also reported an aneurysm in the right sinus of Valsalva, which he ascribed to lack of support from the septum which had been weakened by an old ulcerative lesion just below the valve.

Pathology.—Mycotic embolic aneurysms are found most often in those cases of infective endocarditis with particularly luxuriant and ragged vegetations on the heart valves. Widespread embolism is usually a feature of these cases, and often other arteries are plugged with emboli beside those in which aneurysms are present. Infarcts in the spleen or kidneys, or both, have also been observed in most cases. Occasionally, at necropsy, emboli can still be found in the aneurysms, and in a few cases it has been possible not only to show their resemblance to vegetations on the heart valves but also to find the places from which they were detached. In most cases, the embolus can no longer be found, probably because of disintegration.

Since most mycotic aneurysms occur before the age of 40, it is usual to find the vascular apparatus in excellent condition, except for the localized mycotic lesions. Many writers have commented on the fact that the arteries in their cases appeared normal until one came on an area of ulceration or an aneurysm with sharply delimited edges.

48. Libman: Am. J. M. Sc. **144**:313, 1912.
49. Gilewski: Wien. med. Wchnschr., p. 524, 1868.
50. Hart: Virchows Arch. f. path. Anat. **182**:167, 1905.
51. Kraus: Berl. klin. Wchnschr. **39**:1161, 1902.

This abrupt transition from normal artery to aneurysm is in striking contrast to the condition of the vessels in the neighborhood of syphilitic aneurysms.

On account of their widespread incidence throughout the body with different types of tissues surrounding them, and the wide range in the acuteness and destructiveness of the inflammatory processes present, mycotic aneurysms vary greatly in size, appearance and other characteristics. As a rule, they are much smaller than syphilitic aneurysms. It is rare even in the largest vessels to find one bigger than a walnut, except in the case of false aneurysms, which may be much larger. In the small vessels of the brain, they may be the size of a millet seed or a split pea or even smaller. Often they will not be found unless specially looked for, on account of their minute size or owing to the fact that their thin walls have become practically disintegrated.

Owing to the destructiveness of the inflammatory processes, mycotic aneurysms are prone to rupture. To this fact, and also the rupture of arteries even before aneurysm formation, is due the large number of false aneurysms found with their sacs consisting of compressed perivascular tissue or sometimes with a layer of adventitia partially surrounding a hematoma communicating with the lumen of a vessel. This type of aneurysm is found most frequently in the peripheral arteries. In such locations as the brain, the abdominal cavity or the arch of the aorta, rupture of an arterial wall is much more liable to be followed by free bleeding, so that the ventricles of the brain, the pericardium, a pleural sac or the peritoneal cavity may be found filled with blood. But even in the mesenteric artery there may be a tiny perforation and the formation of a false aneurysm.

In the aneurysms caused by infection from the heart valves, one is liable to find the same type of inflammatory process in the arterial wall as in the valves. Frequently, vegetations have been observed growing about the edges or in the depths of aneurysms; sometimes they are so luxuriant as actually to fill the sac. As a rule, there is little or no pus formation, but the disintegration of the vessel wall may be fairly rapid, and attempts at repair are pretty much in abeyance. However, in the less active subchronic types of inflammation, reparative processes are more in evidence and the wall of the aneurysm may be definitely thickened as in our Case 1. The aneurysms occurring in bacteremias not associated with endocarditis tend to be more acute and abscesses of the artery wall are more often found. In Vanzetti's [52] case and also in others, the walls of the abscesses that had given rise to the aneurysms

52. Vanzetti: Quoted from review by O. Barbacci, Centralbl. f. allg. Path. u path. Anat. **19**:984, 1908.

were still present. In these cases the inflammatory process is usually highly destructive and quickly causes disintegration of the arterial wall and perforation.

The intima is usually intact to the edge of the aneurysm and occasionally covers the margin and extends a short distance into the depth of the aneurysmal sac. It is never found intact over the floor of an aneurysm during the active inflammatory stage. Occasionally, when infection begins in the depths of a vessel, there may be rupture of the intima with the formation of a mere slit entirely concealing the aneurysm underneath (Osler,[2] J. McCrae[39]). The combination of endarteritis, ulceration and small aneurysms seem in some cases, particularly in the aorta, may give the vessel a moth eaten appearance (McNeill[53]).

Various stages of the inflammatory process may be found in different parts of the aneurysm, such as healing on one side and recrudescence of infection on the other, leading to enlargement of the sac or to rupture. In cases of multiple aneurysms, destructive processes may predominate in one aneurysm and reparative processes in another. The type of healed mycotic aneurysm described by Eppinger[3] in which the floor of the sac has been covered over by a smooth lining membrane continuous with the intima is apparently very rare, although it had occurred in our Case 2 and to a certain extent in our Case 1. In peripheral arteries, if healing takes place, there is liable to be an obliteration of the aneurysmal sac and the lumen of the artery as well. In Sanne's case calcification of the edges of the aneurysm occurred.

In spite of the tendency of mycotic aneurysms to rupture, arteriovenous aneurysms have been described only by Simmonds,[54] Libman[20] and Floyd.[55] In Simmonds case there was an aneurysm of the aorta near the bifurcation with a sac that had ulcerated into the right iliac vein. Libman found a communication between the sac of a femoral aneurysm and the femoral vein. In this case the diagnosis of arteriovenous aneurysm was made clinically. Floyd's case was quite similar to Libman's.

Erosion of bone has been reported, so far as we are aware, only once. In this case, described by Libman,[20] an aneurysm of the femoral artery eroded the femur.

Histology.—The histologic pictures vary as widely as the gross appearances. The most characteristic findings are loss of the intima, destruction of the elastic tissues, particularly the internal elastic lamina,

53. McNeill: Southern M. J. **7**:540, 1914.
54. Simmonds: München. med. Wchnschr., p. 627, 1904.
55. Floyd: Surg., Gynec. & Obst. **33**:560, 1921.

and acute or subacute periarteritis and mesarteritis. In the more acute cases micro-organisms are often found in enormous masses.

In some cases the transition from uninvolved vessel to the aneurysmal process is abrupt. In others, undermining of the inflammatory process is found out into the vessel wall that grossly appears normal. The intima may be flush with the edge of the aneurysm, destroyed for a distance beyond the dilated area or, on the other hand, may be found extending down a short way into the aneurysm. The elastic tissue is always badly damaged and the internal elastic lamina is destroyed (Fig. 3, Case 2). Apparently, it is weakened by the infection and finally ruptures. The media muscularis may be destroyed either partially or completely; complete destruction occurs more frequently in the smaller arteries. The changes in the adventitia vary from comparatively little damage to complete destruction with the wall of the aneurysm formed by perivascular tissues.

In the more acute aneurysms, there may be marked infiltration with polymorphonuclear leukocytes; microscopic abscesses are not uncommon. In some cases, such as those of Moriani,[46] Klotz [26] and McNeill [53] the inflammatory process seemed to be centered particularly about the vasa vasorum. When the inflammation is less acute, the cellular infiltration may consist of small round and plasma cells which are seen especially in the adventitia and about the vasa vasorum. Often there are many fibroblasts. At a later stage the artery structure is lost and the wall of the aneurysm consists mainly of fibrous tissue. Areas of poorly staining hyaline-like material are found and there may be calcification. The vasa vasorum tend to be thickened and some are entirely obliterated. Fragments of elastic tissue may still be present. Our Case 2 is probably the best instance of repair of a mycotic aneurysm thus far described.

Clinical Manifestations and Diagnosis.—Usually patients are already under medical observation before the development of mycotic aneurysms, on account of illness, due either to infective endocarditis or some other serious infection. Thus in many cases reported, there has been opportunity to note from the beginning whatever clinical phenomena presented themselves.

In the vessels of the extremities or other superficial arteries where it is possible to study the clinical course of the aneurysms, the most striking feature observed has been their rapid evolution. The onset may occur in a variety of ways. Most frequently the phenomena of embolism are observed first and then in the course of a few days to several weeks aneurysm develops. Embolism, though present, may be overlooked and the condition of the vessel not suspected until a pulsating tumor has manifested itself. Attention is sometimes directed

to a part by pain; on examination there may be only slight swelling or tenderness. Such cases have been mistaken for phlebitis (as in our Case 3), but when tumor and pulsation develop, the error is easily recognized.

Some of the aneurysms rapidly go on to rupture so that the entire course from the beginning of symptoms may last only a week or two, but more often rupture does not occur for several weeks. In peripheral arteries, it may be manifested clinically by rapid enlargement of the tumor which tends to become somewhat boggy and indistinct in outline. Pulsation may still be present. With free rupture, the swelling usually becomes tense and painful. In the cases that do not go on to rupture, the aneurysmal process may become quiescent or apparently healed with a persistence of the tumor and pulsation, as in our Case 4, or as in our Case 3 and Unger's [12] case, the clinical evidences may disappear entirely.

Pain, especially during the period of development of the aneurysm, may be severe, and the part affected may be hot and tender, but these symptoms tend to subside as the process grows older. The tumor in the larger vessels is often stated to be the size of a hen's egg or even larger, but the aneurysms themselves are usually smaller, the mass being made up partly of the surrounding inflamed tissues or sometimes of a hematoma about the aneurysmal sac due to a small rupture. Expansile pulsation is present, often even in false aneurysms. Pulse is usually absent distal to the aneurysm. The circulation in the tissues supplied by the artery affected may be interfered with seriously, but gangrene has been reported in surprisingly few cases.

When superficial arteries are affected, the diagnosis is easy in typical cases. The development of localized tumor and characteristic pulsation along the course of an artery and blockage of blood flow distal to the tumor, occurring in a patient with a septic type of infection, particularly endocarditis, is scarcely to be mistaken for any other condition. It may not be possible to differentiate between true and false aneurysms, but this is of no particular clinical importance. In the early stages, the condition may escape detection or, as stated above, be mistaken for venous thrombosis.

In mycotic aneurysms of the thoracic or abdominal arteries, it is exceptional for signs to develop from which the diagnosis can be made or even suspected. This is to be expected, in view of the small size of most of the aneurysms. The first intimation of the condition may be a sudden fatal hemorrhage and commonly it is, as Jordan found in his case "a post-mortem surprise."

Out of sixty cases in which the root or arch of the aorta has been found at necropsy to be the seat of mycotic aneurysms, our Case 1 is the only one in which a clinical diagnosis was made. The reasons for

this diagnosis have been discussed above. In Sanne's [56] case, a diagnosis of dilatation of the arch was made and in Lauenstein's [57] case, there was believed to be inflammation of the beginning of the aorta but not aneurysm. A clinical diagnosis was made by Baginsky [58] in his case of abdominal aortic aneurysm. The patient developed a pulsating mass in the midabdomen over which a bruit could be heard, previous to which she had shown evidences of septic infection and embolism in the right subclavian artery. In Alexejew's [59] case, there was a palpable pulsation under the umbilicus and the pulse in the left femoral artery was smaller than in the right.

There are to be found in the literature clinical reports of about twenty cases in which the diagnosis was made of aneurysm of the arch of the aorta due to acute rheumatism or chorea. These observations are encountered principally in the French literature, but there are a few from this country and also from Germany. The aneurysms are described as occurring mostly in children or young adults with aortic regurgitation and a history of one or more attacks of rheumatism or chorea. In some of the cases there was thought to be diffuse dilatation of the arch and in others localized ectasis. It is unfortunate that among the patients who died, no necropsies were made. In view of the degree of simple dilatation of the arch that may develop merely as the result of aortic regurgitation, particularly in the young, the diagnosis of aneurysm should be accepted with great caution in such cases, if at all. The most convincing case of the group is the one reported by Bernert [60] in which signs of endocarditis were limited to the mitral valve and the fluoroscope showed spherical dilatation and pulsation of the descending arch.

Aneurysmal dilatation of the pulmonary artery was diagnosed clinically and the diagnosis confirmed at necropsy in cases of mycotic infection of the vessel by Buchwald [19] and Salen.[61] In Salen's case, the roentgen ray showed dilatation of the pulmonary artery, but in Buchwald's case, the diagnosis was made on the clinical findings alone.

Mycotic aneurysm of the mesenteric artery has been diagnosed several times, based on the finding of a pulsating tumor that either could be pushed about the abdomen or might be found first on one side and later on the other, occurring in a patient with infective endocarditis. A bruit over the tumor has also been found of diagnostic value. In one case, masses felt per rectum proved to be mesenteric aneurysms.[20]

56. Sanne: Rev. Mens. des mal. de l'enf. **5**:56, 1887.
57. Lauenstein: Deutsch. Arch. f. klin. Med. **17**:242, 1876.
58. Baginsky: Berl. klin. Wchnschr. **1**:144, 1908.
59. Alexejew: Quoted from Le Boutillier, Am. J. M. Sc. **125**:778, 1903.
60. Bernert: Ztschr. f. klin. Med. **69**:121, 1909-1910.
61. Salen: Acta Med. Scand. **55**:631, 1921.

One patient was operated on for supposed ruptured gastric ulcer and a bleeding mesenteric aneurysm was found.[62] In another case, mesenteric aneurysm was mistaken for abdominal aortic aneurysm.

No clinical diagnosis of mycotic aneurysms involving the other abdominal visceral arteries has been reported. In hepatic aneurysms the symptoms of pain over the region of the liver, jaundice and bleeding into the gastro-intestinal tract have been observed. The occurrence of these symptoms in a patient with a septic infection should strongly suggest the possibility of mycotic aneurysm of branches of the hepatic artery within the liver.

Intracranial mycotic aneurysms have not been diagnosed clinically. In many cases, no symptoms were discovered that could be related to the aneurysms found at necropsy. Clinical signs, when present, have been merely those of embolism, intracranial hemorrhage or both.

Treatment.—Possibility of treatment is limited almost entirely to the aneurysms involving superficial arteries, although in a case reported by Stern,[62] a mycotic mesenteric aneurysm was successfully operated on.

The line of treatment to be adopted should be chosen with due regard to the character of the underlying infection. When the infection was mild or had already subsided, ligation of the artery affected or extirpation of the aneurysm has been performed several times, apparently with good results, but at least one fatality has been recorded incident to operation in such a case. In the cases of typical subacute infective endocarditis with its practically hopeless prognosis, attempts at therapy should be directed mainly toward the comfort of the patient. This can often be best secured by avoidance of operative measures. Under such a regimen as rest to the part, local applications and sedatives as required to relieve pain, the aneurysms will sometimes retrogress or disappear entirely (as in our Case 3). The old treatment of compression of the artery above the aneurysm has been beneficial in some cases. Operation may be necessary for the relief of pain or for rupture of the aneurysm. It may also be advisable if the aneurysmal process continues to progress or threatens to rupture. For the most part, the results of operation have not been very satisfactory. A considerable number of patients have died as a result of the operation or their death has apparently been hastened by it and even those who recovered with a good local result usually died within a short time from their cardiac infection.

SUMMARY

Three unquestionable cases of mycotic aneurysms of intravascular origin and one in which this diagnosis is probable, are reported. The following noteworthy features were exhibited by these cases:

62. Stern: Beitr. z. klin. Chir. **57**:315, 1908.

1. Case 1 is the first to be recorded in which a clinical diagnosis of mycotic aneurysm of the arch of the aorta was confirmed at necropsy.

2. The aortic aneurysm in Case 2 was healed with replacement of destroyed media and intima by a thin layer of young connective tissue covered over by newly formed endothelium which had grown out from the intima at the edges of the aneurysm.

3. In Case 3, all clinical evidences of an unmistakable femoral mycotic aneurysm disappeared.

4. In Case 4, there was a violently pulsating but symptomless aneurysm of the innominate artery that appeared to be healed, in a boy, aged 18, without any evidences of syphilis, but with a history of acute rheumatism and an attack of fever with cardiac involvement.

The cases of mycotic aneurysm of intravascular origin have been collected from the literature [63] and on the basis of this material and our own, the etiology, pathology and clinical manifestations of the condition are discussed.

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63. A complete list of references appears in the reprints.

DISTRIBUTION OF SUGAR IN WHOLE BLOOD, PLASMA AND CORPUSCLES; PERMEABILITY OF RED BLOOD CORPUSCLES FOR SUGAR IN DIABETIC AND NONDIABETIC CASES *

HENRY J. JOHN, M.D.

CLEVELAND

A study of the literature pertaining to the distribution of sugar in the blood shows a decided divergence of opinion among different investigators.

Tachau [1] found that there was always a higher percentage of sugar in plasma and a smaller percentage of sugar in the corpuscles than in whole blood. In a report of their work on the permeability of the red blood corpuscles to sugar, Gradwohl and Blaivas [2] make the following statement: "When the alimentary hyperglycemia begins and sugar is thrown into the circulation in increased quantity, it is first dissolved in plasma and penetrates the corpuscles secondarily. As the hyperglycemia declines, the sugar content of the plasma goes down and the corpuscles then throw their sugar in excess into the plasma. Tachau attempts to explain by this line of reasoning why it is that in the presence of a declining hyperglycemia of alimentary origin the serum loses its sugar and, strange to say, the corpuscles then hold more sugar than the plasma." The conclusions of Gradwohl and Blaivas were based on twenty-four examinations. They found that the amount of sugar in plasma, in whole blood and in corpuscles was nearly the same. They conclude that their studies, which agree with the work of Tachau, seem to disprove some of the theoretic views of the older physiologists who held that a part of the sugar in the blood was in a state of loose combination with some other substance. This obsolete idea had previously been shattered by the work of Rona and Michaelis,[3] who showed that the blood sugar is in a state of solution and that when diluted blood is shaken with certain colloids, such as ferric chlorid or kaolin, the proteins form a colloidal combination and are absorbed. The proteins can be precipitated quantitatively by the addition of a trace of an electrolyte, but no trace of sugar is removed from the solution by this treatment. If the sugar were united with the proteins it would be carried down with them, and as the reagents used cannot have any

* From the Cleveland Clinic.

1. Tachau, H.: Ztschr. f. klin. Med. **79**:421, 1914
2. Gradwohl, R. B. H., and Blaivas, A. J.: J. Lab. & Clin. Med. **2**:416, 1916.
3. Rona and Michaelis: Biochem. Ztschr. **16**:489, 1909; **18**:514, 1909.

TABLE 1.—THE PARTITION OF SUGAR IN THE BLOOD. DIABETIC

Plasma Sugar (100%)	Whole Blood Sugar	Per Cent. Increase or Decrease	Corpuscle Sugar	Per Cent. Increase or Decrease	Corpuscle Volume	Plasma Sugar (100%)	Whole Blood Sugar	Per Cent. Increase or Decrease	Corpuscle Sugar	Per Cent. Increase or Decrease	Corpuscle Volume
114	117	+ 2	117	+ 2		347	321	— 7	300	—13	31
179	183	2	171	— 5	35	279	267	— 4	300	—28	40
400	411	+ 3	352	—12	50	203	210	+ 3	171	—16	40
567	519	— 9	460	—19	55	300	237	—21	242	—20	40
598	578	— 2	464	—22	51	364	354	— 3	272	—25	39
645	598	— 8	500	—22	46	377	420	+11	322	—15	36
579	506	—12	428	—26	52	405	394	— 3	334	—17	41
506	486	— 4	414	—18	52	230	241	+ 5	196	—16	40
424	455	+ 7	364	—14	49	373	335	—10	294	—21	35
98	114	+17	...	....	43	437	422	— 3	334	—23	39
124	125	+ 1	...	....	45	511	515	....	400	—21	41
159	136	—15	...	....	47	557	530	— 5	444	—20	37
136	131	— 4	...	....	46	356	356	....	300	—16	38
155	172	+11	...	....	44	233	229	— 2	179	—23	46
148	159	+ 7	...	....	44	323	315	— 3	260	—20	46
286	286	....	238	—17	54	376	370	— 1	300	—20	46
335	325	— 3				420	384	— 9	310	—26	40
363	362	....	309	—15	41	265	261	— 1	244	— 8	48
425	394	— 7	375	—12	31	157	175	+12	145	— 8	45
381	381	....	375	— 2	36	237	214	—10	183	—23	48
309	318	+ 3	263	—15	44	383	360	— 6	250	—34	50
271	262	— 3	230	—15	47	421	401	— 5	374	—11	42
414	394	— 5	353	—15	45	485	485	....	374	—23	41
394	394	....	316	—20	44	428	407	— 5	400	— 6	40
425	394	— 8	348	—18	43	273	309	+12	286	+ 4	44
350	350	....	319	— 9	40	350	350	....	300	—14	47
302	269	—11	272	—10	42	491	449	— 8	360	—27	44
198	193	— 2	176	—11	45	563	535	—10	444	—25	39
298	284	— 5	250	—16	47	636	610	— 4	526	—17	38
320	307	— 4	261	—18	43	607	596	— 2	512	—15	40
351	351	....	300	—15	40	530	424	—20	412	—22	47
359	351	— 2	313	—12	41	196	196	....	173	—11	48
279	263	— 5	230	—17	41	315	285	— 9	219	—30	44
148	204	+38	179	+20	38	356	356	....	272	—24	44
262	262	....	224	—15	37	411	411	....	187	—55	47
285	285	....	250	—12	35	310	264	—15	214	—31	43
330	319	— 3	300	— 9	37	237	212	—11	176	—26	40
318	302	— 5	272	—14	36	264	268	+ 1	240	— 9	46
260	254	— 2	230	—12	38	460	428	— 7	360	—22	45
129	135	+ 5	122	— 5	43	460	442	— 4	340	—26	41
202	196	— 3	167	—17	43	512	500	— 2	428	—16	42
233	225	— 4	...	....	38	428	428	....	352	—18	42
291	315	+ 8	258	—11	37	342	334	— 2	272	—21	44
308	291	— 5	263	—15	41	250	268	+ 8	200	—20	47
296	312	+ 5	261	—12	42	334	334	....	294	—12	47
344	328	— 5	256	—25	40	460	408	—11	400	—13	50
449	434	— 3	352	—21	42	214	214	....	222	+ 3	41
510	506	— 1	384	—25	40	136	145	+ 6	234	+72	
464	506	+12	404	—13	41	230	214	— 7	200	—13	36
210	202	— 4	172	—18	35	250	250	....	230	— 8	36
262	268	+ 2	230	—12		297	297	....	206	—30	33
350	350	....	285	—19	33	155	154	....	143	— 8	42
379	353	— 7	319	—16	33	286	290	+ 1	219	—24	42
324	315	— 3	256	—21	35	374	334	—10	268	—28	38
115	115	....	116	+ 1	48	368	366	....	310	—16	39
145	145	....	150	+ 3	59	306	250	—18	240	—21	40
209	217	+ 4	196	— 6	43	210	187	—11	176	—16	39
175	159	— 9	180	+ 2	38	192	182	— 5	158	—18	38
86	110	+28	106	+23	43	346	316	— 9	244	—30	40
202	239	+18	224	+11	47	352	334	— 5	294	—16	40
308	312	—15	265	—28	43	280	340	+21	261	— 7	36
324	284	—12	265	—18	44	238	243	+ 2	186	—22	43
358	315	—12	294	—18	43	184	187	+ 2	173	— 6	42

TABLE 2.—THE PARTITION OF SUGAR IN THE BLOOD. NONDIABETIC

Plasma Sugar (100%)	Whole Blood Sugar	Per Cent. Increase or Decrease	Corpuscle Sugar	Per Cent. Increase or Decrease	Corpuscle Volume	Plasma Sugar (100%)	Whole Blood Sugar	Per Cent. Increase or Decrease	Corpuscle Sugar	Per Cent. Increase or Decrease	Corpuscle Volume
89	108	+21	116	+30	38	156	156	....	105	−33	48
163	182	+11	164	+ 0.5	42	124	125	+ 1	88	−29	42
149	150	+ 7	156	+11	43	124	124	....	120	− 3	52
128	129	+ 0.5	131	+ 2	45	92	95	+ 3	94	+ 2	41
95	105	+10	134	+41	44	64	84	+31	120	+87	43
98	104	+ 6	104	+ 6	49	98	102	+ 4	104	+ 6	47
94	124	+32	117	+24	38	163	161	− 1	153	− 6	39
155	171	+10	167	+ 8	47	133	132	− 1	120	−10	
188	176	− 6	152	−19	51	131	131	....	126	− 4	39
168	160	− 5	136	−19	57	53	78	+47	75	+40	38
114	119	+ 5	120	+ 5		72	86	+19	85	+18	39
109	108	− 1	133	+22	48	108	111	+ 8	104	+ 1	35
98	98	....	...	.....	48	159	...	....	145	− 9	30
146	141	− 3	...	.....	43	202	200	+ 4	176	−13	34
177	177	....	...	.....	39	136	150	+10	127	− 7	35
122	143	+ 8	...	.....	41	95	95	....	107	+12	34
75	81	+ 8	...	.....	45	74	76	+ 3	85	+17	34
98	106	+ 8	...	.....	41	191	207	+ 8	176	− 8	43
143	137	− 5	...	.....	43	412	398	− 5	366	−11	42
102	91	−11	...	.....	41	420	405	− 4	324	−23	44
149	134	−10	...	.....	45	203	214	+ 5	200	− 2	45
114	123	+ 8	...	.....	42	80	99	+24	104	+30	41
57	57	....	...	.....	45	117	146	+25	104	−11	42
89	100	+12	...	.....	46	100	110	+10	125	+25	47
101	103	+ 2	...	.....	37	172	166	− 4	147	−15	37
119	119	....	...	.....	39	174	174	....	102	− 7	32
121	121	....	...	.....	44	130	137	+ 5	136	+ 4	37
57	71	+25	...	.....	50	87	102	+17	107	+23	35
50	63	+26	...	.....	40	118	119	+ 1	107	−10	37
104	107	+ 2	...	.....	46	123	143	+16	143	+16	35
164	149	− 5	...	.....	38	256	210	−18	232	−10	38
121	117	− 3	...	.....	42	210	384	+82	187	−11	
91	104	+14	...	.....	40	150	160	+ 7	170	+13	37
50	63	+26	...	.....	38	63	64	+ 1	113	+80	35
40	51	+28	...	.....	38	96	109	+14	120	+25	42
111	111	....	...	.....	36	128	128	....	107	−16	39
160	160	....	...	.....	36	186	183	− 1	154	−17	47
228	225	− 2	...	.....	38	204	197	− 4	176	−14	
222	216	− 2	...	.....	36	205	138	−33	187	− 9	47
69	80	+16	...	.....	38	125	125	....	151	+21	50
108	118	+ 9	...	.....	46	145	112	−23	85	−41	45
131	150	+15	...	.....	43	125	134	+ 7	...	....	51
185	180	− 3	...	.....	40	183	200	+ 9	187	+ 2	41
106	123	+16	...	.....	40	172	167	− 3	141	−18	39
79	88	+12	...	.....	38	102	102	....	150	− 8	38
67	78	+16	...	.....	42	107	107	....	105	− 2	38
126	126					75	88	+18	94	+25	34
148	161	+ 9	128	−14	53	128	120	− 6	124	− 3	42
121	148	+22	128	+ 6	51	207	196	− 5	176	−15	45
116	142	+22	129	+11	50	146	158	+ 8	158	+ 8	35
104	60	−42	104	....	44	125	133	+ 6	136	+ 9	39
115	79	−31	116	+ 1	51	107	100	− 6	116	+ 8	37
95	102	+ 7	111	+16	35	79	81	+ 2	102	+29	37
167	177	+ 6	150	−10	32	110	111	+ 1	114	+ 3	47
167	177	+ 6	...	.....	30	150	150	....	150	....	47
102	127	+24	146	+44	64	156	143	− 8	141	−10	42
71	79	+11	94	+32	33	136	141	+ 4	206	+50	44
85	116	+37	111	+30	31	106	...	....	133	+25	42
94	108	+15	130	+38	42	64	83	+30	...	....	35
171	164	− 5	158	− 8	44	125	...	....	141	+13	38
175	178	+ 1	172	− 2	47	222	230	+ 3	206	− 7	35
53	53	....	52	− 2		230	116	−50	236	+ 3	31
78	78	....	...	.....	24	155	158	+ 2	200	+29	23
92	109	+18	103	+12	47	104	...	....	158	+52	
102	102	....	94	− 8	52	54	83	+54	...	....	38
158	151	− 5	136	−14	52	98	94	− 4	94	− 4	33
104	123	+18	111	+ 7		158	158	....	156	− 1	38
109	111	+ 1	120	+10	38	121	122	+ 1	122	+ 1	38
65	69	+ 6	100	+54	44	147	136	− 8	129	−12	39
91	104	+14	94	+ 3	55	111	120	+ 8	118	+ 6	35
107	104	− 3	104	− 3	47	82	82	....	88	+ 7	39

disruptive effect, the proof is complete that it is not possible for the sugar to exist in combination with the proteins.

Cammidge [4] states that further evidence of the existence of dextrose in the blood in a free state is furnished by the observation that although charcoal when shaken with a solution containing both sugar and protein absorbs these two substances, it absorbs only the protein when acetone is present. That is, the acetone, being more capable of absorption than the dextrose, prevents the latter from being taken up by the charcoal. Further evidence of this conclusion is also furnished by the results of dialysis experiments.

TABLE 3.—Permeability of Red Blood Corpuscles to Sugar. Diabetic Corpuscles Exposed to Action of Glucose 1,000 mg./100 c.c. Made Up in Physiologic Solution of Sodium Chlorid

Date	Plasma Sugar	Corpuscle Sugar	2 Hours	Per Cent.
April 20	270	202	272	137
		280	544	194
	212	187	576	308
	219	171	526	308
	182	142	600	422
	182	155	544	350
April 20	161	...	564	350
	280	155	526	339
	204	162	544	336
	187	187	564	302
	171	146	544	373
	129	111	554	499
April 21	236	214	500	234
	330	...	504	153
	333	316	584	185
	275	333	560	168
	230	316	504	160
	313	248	576	232
April 28	130	124	500	405
	156	150	516	344
	174	145	500	346
	265	230	500	217
	288	252	500	199

Masing [5] has shown by exhaustive experiments that when sugar is added to a quantity of blood in vitro the corpuscles first take up the sugar but later give it up so that most of the sugar is finally found in the plasma. This is a confirmation of the work of Rona [6] and of the earlier work of Masing himself. Masing showed further that the addition of sugar to blood was followed by the slow entrance of sugar into the corpuscles at 0 C. and by a more rapid entrance at 25 C., this entrance being hindered markedly by a high temperature. Masing also showed that treatment of corpuscles with liquor formaldehydi enhanced their permeability for sugar.

4. Cammidge, P. J.: Glycosuria and Allied Conditions, Longmans, Greene & Co., 1913, p. 19.
5. Masing, E.: Arch. f. d. ges. Physiol. **149**:227, 1912.
6. Rona and Döblin: Biochem. Ztschr. **31**:215, 1911.

TABLE 4.—Permeability of Red Blood Corpuscles to Sugar. Nondiabetic Corpuscles Exposed to Action of Glucose 1,000 mg./100 c.c. Made Up in Physiologic Solution of Sodium Chlorid

Date	Plasma Sugar	Corpuscle Sugar	1 Hour	Per Cent.	2 Hours	Per Cent.	3 Hours	Per Cent.
April 1	89	92	472	514	...	...	500	545
2	97	80	414	466	...	...	476	535
7	88	96	...	...	544	566		
	152	155	...	...	544	353		
	189	162	...	...	544	336		
	173	146	...	...	460	316		
	83	104	...	...	522	502		
	67	75	...	...	516	688		
10	125	120	...	...	278	232		
	186	170	...	...	416	245		
	197	199	...	...	464	233		
	124	129	...	...	442	343		
11	95	88	...	...	428	488		
	133	130	...	...	434	333		
	158	136	...	...	434	318		
	128	136	...	...	424	312		
12	65	72	434	600	444	616	452	630
13	73	73	...	...	452	620		
	109	107	...	...	454	424		
	105	94	...	...	426	453		
	70	73	...	...	454	622		

TABLE 5.—The Partition of Sugar in the Blood. Corpuscular Sugar

	Number of Cases			
	Increase		Decrease	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
5 per cent.	12	6	10	3
10 per cent.	11	1	15	12
15 per cent.	6	1	10	28
20 per cent.	4	1	5	30
25 per cent.	8	1	1	21
30 per cent.	5	..	1	12
35 per cent.	1	..	1	2
40 per cent.	2	..	..	..
45 per cent.	2	..	1	..
50 per cent.	1	..	..	..
Above 50 per cent.	4	..	..	1

TABLE 6.—The Partition of Sugar in the Blood. Whole Blood Sugar

	Number of Cases			
	Increase		Decrease	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
5 per cent.	19	14	15	38
10 per cent.	17	4	5	19
15 per cent.	5	4	..	9
20 per cent.	6	1	1	2
25 per cent.	6	1	1	1
30 per cent.	..	1	..	..
35 per cent.	2	..	2	..
40 per cent.	1	1	..	..
45 per cent.	..	..	1	..
50 per cent.	1	..	1	..
Above 50 per cent.	1	..	..	..

Bailey [7] concludes that blood sugar is divided equally between the plasma and the corpuscles, and that the sugar in the corpuscles bears a direct relation to that in the plasma. Wishart [8] finds that normally the concentration of sugar in the corpuscles is a little below that in the plasma. This discrepancy becomes greater as the amount of blood sugar rises. She did not confirm the statement that in the declining stages of hyperglycemia the corpuscles retain their sugar longer than the plasma; and explains the lower sugar content in the corpuscles on

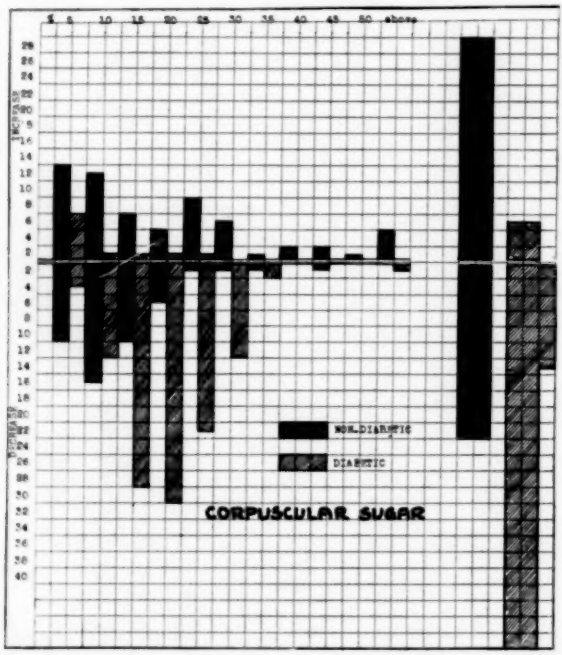

Chart 1.—Comparison of the corpuscular sugar in diabetics and in nondiabetics. The solid black and the shaded columns indicate the number of nondiabetic and of diabetic cases, respectively, in which the corpuscular sugar was increased or decreased as compared with the sugar content of the plasma. The cases were grouped according to the percentile increase or decrease as noted at the top of the chart. The sum total of the increases and decreases in each type of case is shown by the black and shaded columns at the right of the chart.

the ground that sugar is more soluble in the plasma than in the corpuscle substance, owing, no doubt, to the lipoidal content of the latter.

7. Bailey, C. V.: Arch. Int. Med. **23**:455 (April) 1919.
8. Wishart, M. B.: J. Biol. Chem. **44**:563, 1920.

The group of cases reported here consists of a series of diabetic and nondiabetic subjects on whom glucose tolerance tests were made. In each case enough blood was taken to allow for estimations of the blood sugar in the plasma and corpuscles as well as in the whole blood. The corpuscles were not washed. The blood was centrifuged at high speed for fifteen minutes after which the plasma was drawn off and 1 c.c. of the corpuscles was taken for sugar estimation. Myers' modification of Benedict's method of blood sugar estimation was used, the readings being made by means of the Kober colorimeter. In all of

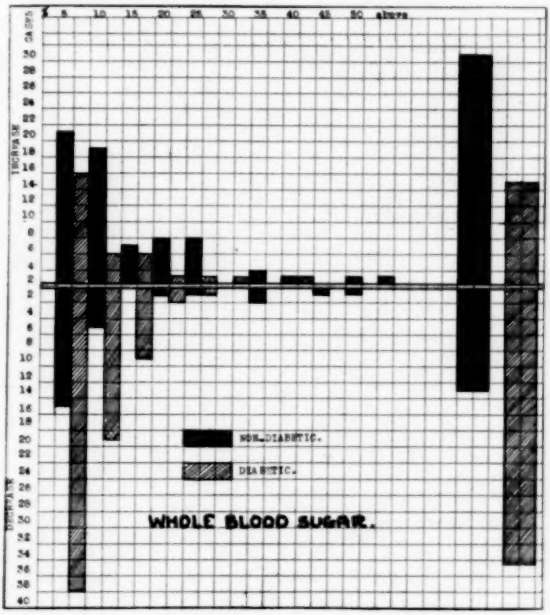

Chart 2.—Comparison of the sugar content of whole blood in diabetics and in nondiabetics. The increase or decrease as compared with the sugar content of the plasma is indicated as in Chart 1.

our blood sugar studies the plasma content has been taken as the standard, the estimations of the sugar content of the whole blood and of the corpuscles being compared with this. Thus, any reported increase or decrease in the sugar content of the whole blood or of the corpuscles means an increase or decrease as compared with the plasma sugar.

A comparison of Tables 1 and 2, as illustrated in Chart I, shows that in nondiabetics the average increase in the corpuscular sugar is approximately equal to the average decrease, while in diabetics, in the majority

of cases, the corpuscular sugar was decreased. This means that the red blood corpuscles of the nondiabetic may contain either more or less sugar than the plasma, while in the diabetic, on the other hand, the corpuscle sugar content is less than the plasma content, higher corpuscle sugar content being exceptional.

The fact that the sugar content of the corpuscles of a nondiabetic is greater than that of the plasma is rather interesting, as in most reports it is stated that the "corpuscular sugar is below that of the

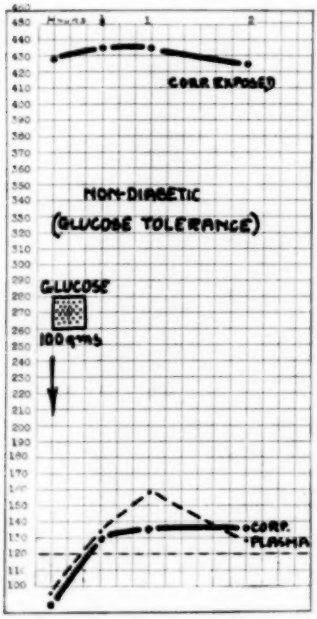

Chart 3

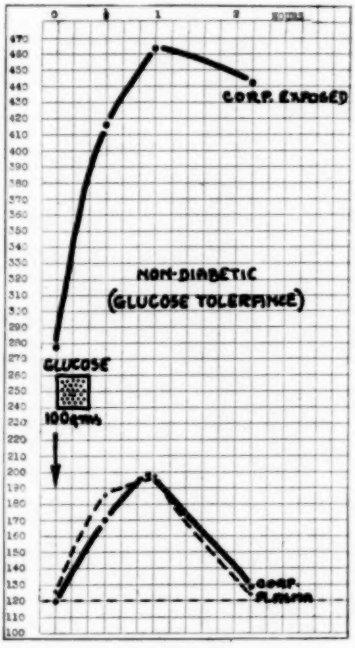

Chart 4

Charts 3 and 4. — Comparison of the glucose tolerance curves of plasma and of corpuscles in nondiabetic cases. The upper curve ("corp. exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg. per hundred cubic centimeters normal solution for a period of two hours.

plasma," no differentiation having been made between diabetic and nondiabetic patients.

The studies of the sugar content of whole blood (Chart 2) represent the midway stage between the sugar content of the plasma and the corpuscular sugar. This chart and Tables 1 and 2 show that in nondiabetics the average increase in the sugar content of whole blood

is greater than the average decrease, while in diabetics the reverse is true, whole blood sugar content being usually decreased.

From these data one would conclude that in the nondiabetic the blood sugar is distributed about equally between the corpuscles and

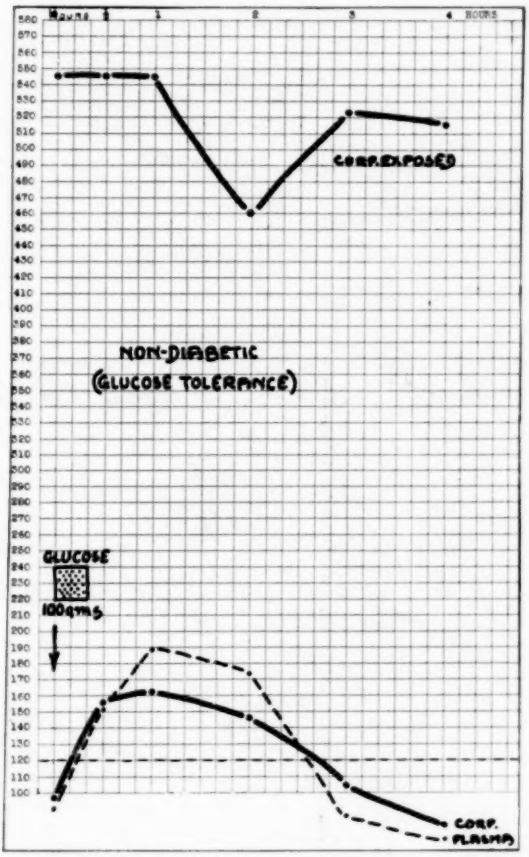

Chart 5.—Comparison of the glucose tolerance curves of plasma and of corpuscles in nondiabetic cases. The upper curve ("corp. exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1.000 mg. per hundred cubic centimeters normal solution for a period of two hours.

the plasma; while in the diabetic, on the contrary, the corpuscles contain less sugar than the plasma which surrounds them. The question which presents itself, therefore, is this: Does this mean that the red blood corpuscles in the diabetic are less permeable to sugar than the

plasma; has the corpuscle membrane been injured in some way so that it is less permeable to sugar just as the renal membrane in untreated cases of diabetes become less permeable to sugar? In attempting to answer this question, my *a priori* reasoning was as follows:

If one were to take the red blood corpuscles of a diabetic and those of a nondiabetic, and were to suspend each in a hypertonic solution of

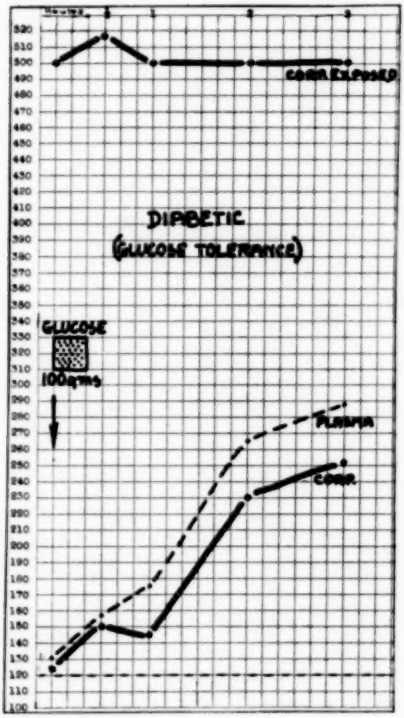

Chart 6

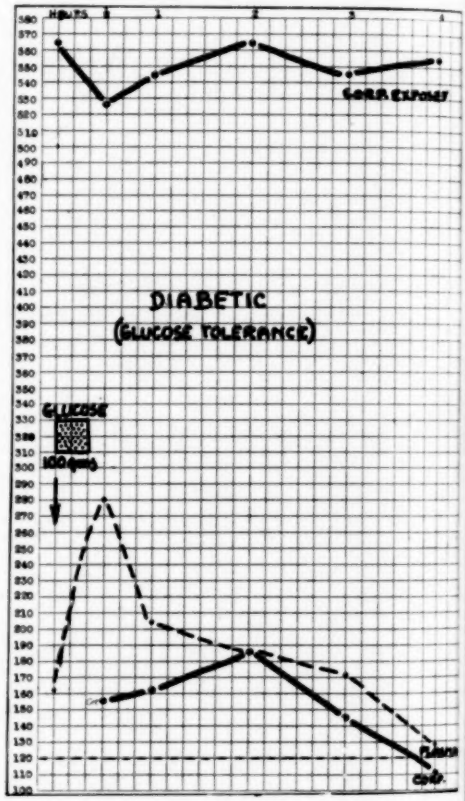

Chart 7

Charts 6 and 7.—Comparison of the glucose tolerance curves of plasma and of corpuscles in diabetic cases. The upper curve ("corp. exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg. per hundred cubic centimeters normal solution for a period of two hours.

sugar in physiologic solution of sodium chlorid to insure isotonicity, what would happen? If the red blood corpuscles of the diabetic are less permeable to sugar than the plasma, it is logical to suppose that at

the end of a certain period they would contain less sugar than those of the nondiabetic. The following experiment was planned to test the value of this reasoning. Whole blood was centrifuged at a high speed; the sugar content of the plasma and of the corpuscles was determined; the remainder of the red corpuscles were then exposed for a period of

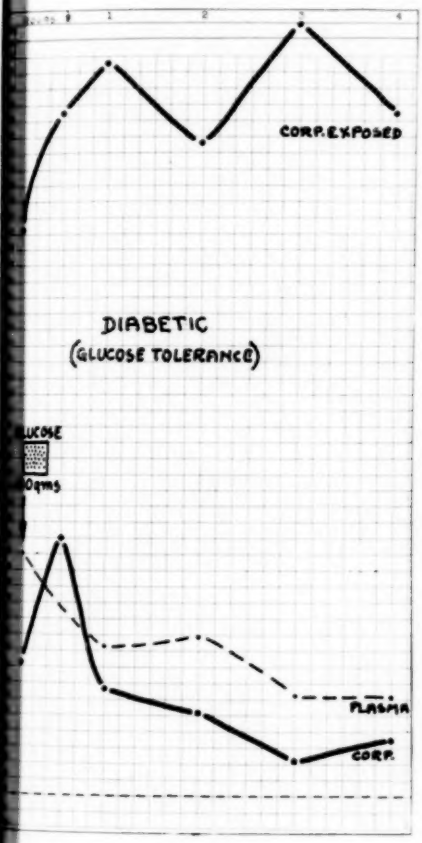

Chart 8

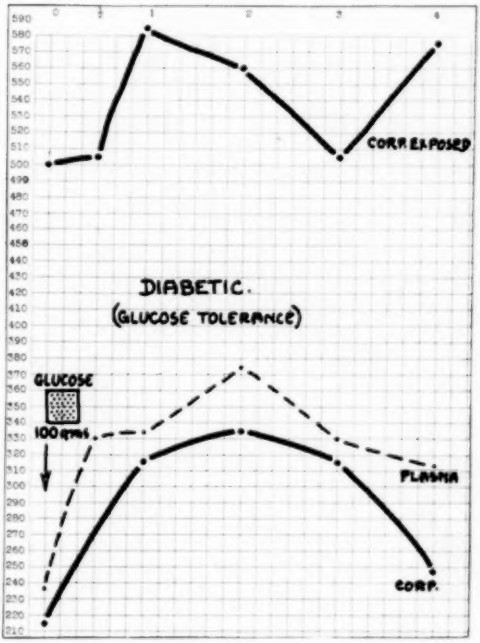

Chart 9

Charts 8 and 9.—Comparison of the glucose tolerance curves of plasma and of corpuscles in diabetic cases. The upper curve ("corp. exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg. per hundred cubic centimeters normal solution for a period of two hours.

two hours to the action of a glucose solution—1 gm. to 100 c.c. of physiologic sodium chlorid solution. At the end of the two hours the corpuscles were centrifuged again at high speed for fifteen minutes and

a sugar estimation was made. The results of the experiment are shown in Charts 3 to 9 and in Tables 3 and 4. As the charts show, with the exception of Case 5, the sugar content of the corpuscles of the diabetics after exposure to glucose solution rose to a much higher level than in the corpuscles of the nondiabetics. An analysis of Case 5 shows that the blood sugar curve (glucose tolerance) returned to the normal level at about the end of the third hour (Chart 5). In this case, therefore, we were dealing with a decreased tolerance, or, in other words, with a prediabetic [9] rather than with a true diabetic.

I am unable to explain this difference between the blood of the diabetic and that of the nondiabetic cases. All I can do is to state the fact that in the blood stream of the diabetic the red corpuscles contain less sugar than the surrounding plasma, and in a strong sugar solution take up more sugar than do the red corpuscles of the nondiabetic. It is my hope that further work may offer an explanation of this phenomenon.

CONCLUSIONS

1. In nondiabetics, after the ingestion of glucose, the sugar in the corpuscles may be either increased or decreased as compared with the plasma content, the tendency to an increase slightly predominating.

2. In diabetics the sugar in the corpuscles is practically always decreased below the plasma content.

3. On exposure of the red blood corpuscles of nondiabetics to a concentration of 1 gm. of glucose in 100 c.c. of physiologic sodium chlorid solution for two hours, the corpuscles take up less sugar than the corpuscles of the diabetics which have been treated in a like manner.

9. John, H. J.: The Prediabetic Stage, Ohio State M. J. **17**:826, 1921.

A STUDY OF BLOOD PRESSURE IN RELATION TO TYPES OF BODILY HABITUS*

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ST. LOUIS

Interest in the correspondence of visceral form, position and tonus to bodily habitus as observed in gastro-intestinal roentgen-ray studies suggested the analysis of some available data as to the relation of blood pressure to bodily habitus.

The conceptions of bodily habitus as followed in this analysis are those formulated by Mills;[1] and they are used in the classification of the subjects of this study. The sthenic type (Fig. 1) is of strong skeletal build, short and deep thorax, relatively broad shoulders, a costal angle of 90 degrees or more, and has a narrow pelvis as between the anterior superior spines of the ilia. The hypersthenic type (Fig. 2) is an accentuation of all the sthenic characteristics, giving a massive build, with short, deep and broad thorax, an obtuse costal angle and narrow pelvis. The torso is massive above. The asthenic type (Fig. 3) is of delicate skeletal build, with long and narrow thorax, very acute costal angle and wide flare of pelvis. The torso is large below. The hyposthenic type (Fig. 4) follows closely the sthenic characteristics, but these are not so definite and the general build is less rugged.

Classification is made difficult by transitional types. All subjects are not pure sthenics or asthenics, and classification by the external topographic criteria only assumes that topography and tonicity are inseparable in their hereditary transmission.

Stiller cites the movable tenth rib as a positive stigma of the asthenic constitution. However, Kastner,[2] in a small group of cases selected by this sign, found no constant agreement between it and the asthenic form and position of the stomach. It is conceivable that heredity can endow a person with topographic characteristics tending toward the sthenic type, but hold a dominant asthenic characteristic of tonicity.

The subjects for this study were unselected applicants for factory work, and their previous occupation is unknown. Classification of each subject was made prior to taking his or her blood pressure. The blood pressure readings were all made under uniform conditions; at the same time of day; with the same mercury column instrument; the subject in the sitting posture, using the right arm, and by the auscultatory method.

* Read before the Washington University Medical Society, May 8, 1922.

1. Mills, R. W.: The Relation of Bodily Habitus to Visceral Form, Position, Tonus and Motility, Am. J. Roentgenol. **4**:155 (April) 1917.

2. Kastner: Movable Tenth Rib as an Enteroptotic Stigma, Arch. f. klin. Chir. **117**:737, 1921.

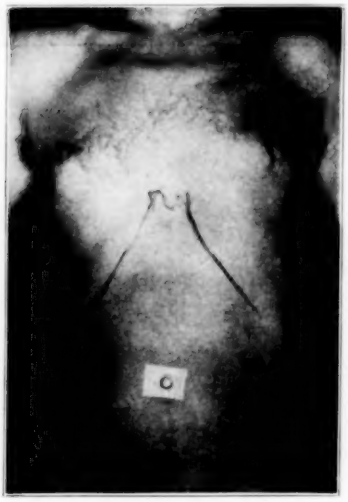

Figure 1

Figure 2

Fig. 1.—The Sthenic Habitus (From Mills, courtesy of Am. J. Roentgenol.).

Fig. 2.—The Hypersthenic Habitus (From Mills, courtesy of Am. J. Roentgenol.).

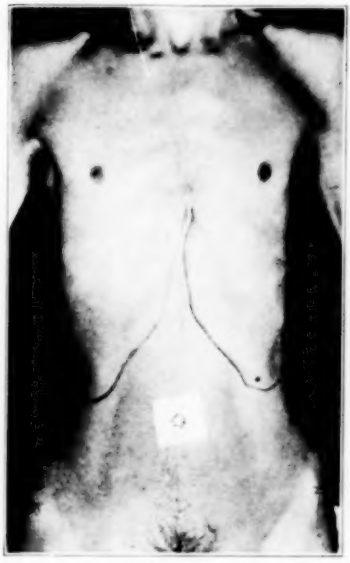

Figure 3

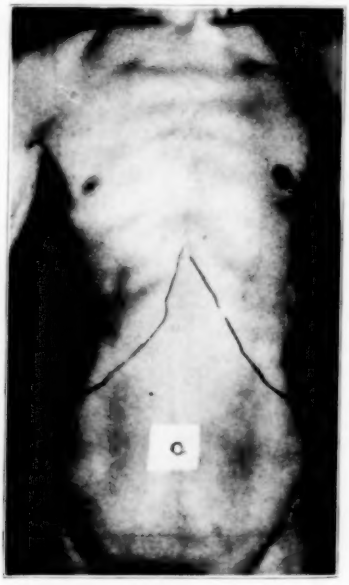

Figure 4

Fig. 3.—The Asthenic Habitus (From Mills, courtesy of Am. J. Roentgenol.).

Fig. 4.—The Hyposthenic Habitus (From Mills, courtesy of Am. J. Roentgenol.).

TABLE 1.—MALES: BLOOD PRESSURE VARIATIONS OF DIFFERENT TYPES

Blood Pressure Mm. Hg Systolic:	Hypersthenics 2, Number	Sthenics, 82 Number	Sthenics, 82 Per Cent.	Hyposthenics, 76 Number	Hyposthenics, 76 Per Cent.	Asthenics, 19 Number	Asthenics, 19 Per Cent.	Total, 179 Number	Total, 179 Per Cent.
151–160	..	3	3.6	..	....	..	....	3	1.6
141–150	..	5	6.1	1	1.3	..	....	6	3.3
131–140	2	18	21.9 *	5	6.5	..	....	25	13.9
121–130	..	31	37.8	16	21.1	2	10.5	49	27.4
111–120	..	17	20.7	36	47.3	2	10.5	55	30.7
101–110	..	8	9.7	14	18.8	13	68.3	35	19.5
91–100	..	..	....	4	5.2	1	5.2	5	2.8
81– 90	..	..	....	..	....	1	5.2	1	0.5
Diastolic:									
91–100	1	3	3.6	..	....	..	....	4	2.2
81– 90	..	23	28.0	4	5.2	..	....	27	15.0
71– 80	1	38	46.3	27	35.5	1	5.2	67	37.4
61– 70	..	12	14.6	36	47.3	11	57.8	59	32.9
51– 60	..	5	6.1	9	11.8	7	36.8	21	11.7
41– 50	..	1	1.2	..	....	..	....	1	0.5

* Bracketed percentages indicate the groups selected for analysis in Table 3.

TABLE 2.—FEMALES: BLOOD PRESSURE VARIATIONS OF DIFFERENT TYPES

Blood Pressure Mm. Hg Systolic:	Hypersthenics, 1, Number	Sthenics, 106 Number	Sthenics, 106 Per Cent.	Hyposthenics, 69 Number	Hyposthenics, 69 Per Cent.	Asthenics, 62 Number	Asthenics, 62 Per Cent.	Total, 238 Number	Total, 238 Per Cent.
151–160	..	1	0.9	..	....	..	....	1	0.4
141–150	1	2	1.8	1	1.4	..	....	3	1.2
131–140	..	12	11.3	8	11.6	2	3.2	22	9.2
121–130	..	45	42.4 *	11	15.9	4	6.4	60	25.2
111–120	..	27	25.4	34	49.2	16	25.8	77	32.4
101–110	..	14	13.2	13	18.8	28	45.2	55	23.1
91–100	..	6	5.6	2	2.9	11	17.7	19	8.0
81– 90	..	..	....	..	....	1	1.6	1	0.4
Diastolic:									
91–100	..	3	2.8	..	....	..	....	3	1.2
81– 90	..	14	13.2	8	11.6	1	1.6	23	9.6
71– 80	1	51	48.1	29	42.0	16	25.8	97	40.8
61– 70	..	32	30.2	25	36.2	36	58.0	93	39.1
51– 60	..	5	5.6	7	10.1	8	12.9	21	8.8
41– 50	..	..	....	..	....	1	1.6	1	1.2

* Bracketed percentages indicate the groups selected for analysis in Table 4.

TABLE 3.—MALES: ARITHMETICAL AVERAGES OF CENTRAL GROUPS

Group Total (Selected According to Blood Pressure)	Total	Average Age	Blood Pressure Systolic	Blood Pressure Diastolic	Blood Pressure Pulse	Body Surface, Sq. M.
Sthenics	82	..	111–140	61–90		
	100%		80.4%	88.9%		
Hyposthenics	76	..	101–130	61–80		
	100%		87.2%	82.8%		
Asthenics	19	..	101–110	51–70		
	100%		68.3%	94.6%		
Total Selected:						
Sthenics	65	..	126.3	78.8	47.5	1.81
Hyposthenics	62	..	116.3	71.7	44.6	1.67
Asthenics	15	..	106.8	63.3	43.5	1.666
17–20 Years:						
Sthenics	7	18	123.1	76.6	46.5	1.703
Hyposthenics	15	18	116.3	68.7	47.6	1.65
Asthenics	7	17.7	104.6	61.7	42.9	1.61
21–30 Years:						
Sthenics	23	25.6	125.6	76.2	49.4	1.83
Hyposthenics	28	25.3	117.0	71.7	45.3	1.658
Asthenics	4	24.2	106.5	65.5	41.0	1.72
31–40 Years:						
Sthenics	23	36.6	126.4	81.2	45.2	1.834
Hyposthenics	15	34	115.0	72.9	42.1	1.746
41–50 Years:						
Sthenics	11	45	129.2	77.3	51.9	1.772

Tables 1 and 2 are numerical tabulations of the charts and show in comparative percentages the downward blood pressure variation of the different types from sthenic to asthenic.

The bracketed percentages indicate the groups selected for analysis (Tables 3 and 4) and represent the central portions of the incidence curves, the extremes of the incidence in the high and low pressures being discarded.

TABLE 4.—FEMALES: ARITHMETICAL AVERAGES OF CENTRAL GROUPS

Group Total (Selected According to Blood Pressure)	Total	Average Age	Blood Pressure			Body Surface, Sq. M.
			Systolic	Diastolic	Pulse	
Sthenics	106	..	101-130	61-80		
	100%		81.0%	78.3%		
Hyposthenics	69	..	101-130	61-80		
	100%		83.9%	78.2%		
Asthenics	62	..	91-120	61-80		
	100%		88.7%	83.8%		
Total Selected:						
Sthenics	68	..	118.4	73.4	45.0	1.61
Hyposthenics	55	..	115.6	72.3	43.3	1.539
Asthenics	51	..	105.7	68.2	37.5	1.506
17-20 Years:						
Sthenics	43	17.7	118.5	71.9	46.6	1.58
Hyposthenics	38	17.8	114.0	70.3	44.7	1.53
Asthenics	30	17.9	103.5	66.9	36.6	1.499
21-30 Years:						
Sthenics	23	24.5	118.0	75.6	42.4	1.66
Hyposthenics	14	22.8	119.7	77.3	42.4	1.56
Asthenics	18	23.1	109.0	69.6	39.4	1.51
31-40 Years:						
Sthenics	2	33	120.0	80.0	40.0	1.64
Hyposthenics	3	34.8	117.3	73.3	44.0	1.56
Asthenics	3	34.6	108.0	73.3	34.7	1.56

TABLE 5.—HABITUS CLASSIFICATION

	Females		Males		Total		Mills' Percentage of 1,000 Cases Males and Females
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	
Hypersthenic	1	0.4	2	1.1	3	0.8	4.7
Sthenic	106	44.5	82	45.8	188	45.1	48.1
Hyposthenic	60	29.0	76	42.4	145	34.6	35.4
Asthenic	62	26.1	19	10.6	81	19.4	11.8
	238		179		417		

Tables 3 and 4 show arithmetical averages for the large central portions of the blood pressure incidence of the different types, and a further separation into groups for age.

There is no significant blood pressure variation between the types associated with their age variation.

There is a definite, though very small, direct correspondence in body surface variation and the decreasing pressure between the types.

Table 5 compares the type percentages in my group to the percentages of a group of 1,000 gastro-intestinal cases, as given by Mills.[3]

3. Mills, R. W.: Two Tables Pertaining to the Incidence of Bodily Habitus and the Time of Complete Gastric Motility in Different Types of Habitus. Am. J. Roentgenol. **9**:731 (Nov.) 1922.

The variation in the type percentages between the male and the female groups suggests that the commonly accepted difference in the male and female blood pressure is due to the predominance of the asthenic type among females, which increases the incidence of lower pressures and hence lowers the averages.

Tables 6 and 7 show in comparative percentages the incidence of subjects in each type according to differences of 0.1 square meter of

TABLE 6.—INCIDENCE OF MALES IN EACH TYPE

Body Surface, Sq. M.	Hypersthenic, Number	Sthenic		Hyposthenic		Asthenic		Total	
		Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
2.31–2.40	2	..	....	..	....	..	....	2	1.1
2.21–2.30	..	..	....	..	....	..	....	..	....
2.11–2.20	..	3	3.6	..	....	..	....	3	1.6
2.01–2.10	..	3	3.6	..	....	..	....	3	1.6
1.91–2.00	..	12	14.6	1	1.3	1	5.2	14	7.8
1.81–1.90	..	18	21.9	18	23.6	3	15.8	39	21.8
1.71–1.80	..	28	34.1	19	25.0	3	15.8	50	27.9
1.61–1.70	..	13	15.8	20	26.3	8	42.1	41	22.8
1.51–1.60	..	5	6.1	14	18.4	2	10.5	21	11.7
1.41–1.50	..	..	....	4	5.2	..	....	4	2.1
1.31–1.40	..	..	....	..	....	2	10.5	2	1.1
	2	82		76		19		179	

TABLE 7.—INCIDENCE OF FEMALES IN EACH TYPE

Body Surface, Sq. M.	Hypersthenic, Number	Sthenic		Hyposthenic		Asthenic		Total	
		Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
2.31–2.40	..	..	....	..	....	..	....	..	....
2.21–2.30	..	1	0.9	..	....	..	....	1	0.4
2.11–2.20	..	0	....	..	....	..	....	0	....
2.01–2.10	..	2	1.8	..	....	..	....	2	0.8
1.91–2.00	..	3	2.8	..	....	..	....	3	1.2
1.81–1.90	..	10	9.4	..	....	..	....	10	4.2
1.71–1.80	1	12	11.3	1	1.4	3	4.7	17	7.1
1.61–1.70	..	26	15.1	15	21.7	10	16.1	51	21.4
1.51–1.60	..	20	28.3	32	46.3	19	30.6	81	34.0
1.41–1.50	..	19	17.9	20	29.0	21	33.8	60	25.2
1.31–1.40	..	3	2.8	1	1.4	9	14.5	13	5.4
	1	106		69		62		238	

body surface. Body surface was determined by the nomographic chart of Boothby and Sandiford.[4] There is a slight decrease in the body surface from the sthenics to the asthenics of this group.

SUMMARY

In a group of 417 factory workers the blood pressure is analyzed for its relation to bodily habitus. In this group the sthenic habitus is accompanied by a higher blood pressure than is the asthenic habitus. The pressure accompanying the hyposthenic habitus is intermediate.

4. Boothby, W. M., and Sandiford, R. B.: Nomographic Charts for the Calculation of the Metabolic Rate by the Gasometer Method, Boston M. & S. J. **185**:337 (Sept. 22) 1921.

The average blood pressures are approximately the same for the male and female asthenics, being 106.8 mm. systolic and 63.3 mm. diastolic for the males and 105.7 mm. systolic and 68.2 mm. diastolic for the females.

The pressures for the hyposthenic groups are also approximately the same, 116.3 mm. systolic and 71.7 mm. diastolic for the males and 115.6 mm. systolic and 72.3 mm. diastolic for the females. The sthenic group shows a higher pressure for the males, 126.3 mm. systolic and 78.7 mm. diastolic, compared to that of the females 118.4 mm. systolic and 73.4 mm. diastolic.

These relations do not change when the types are separated into groups for age decades.

There is a very small direct correspondence between the types for body surface and the decreasing blood pressure.

HEMOGLOBINURIA IN HEMOLYTIC JAUNDICE*

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My purpose in presenting this paper is to supplement the evidence in favor of the occasional occurrence of spontaneous hemoglobinuria in hemolytic jaundice. Three cases of this type in which the diagnosis of hemolytic jaundice is well established and an occasional case of questionable diagnosis have been reported in German and French. However, I have been unable to find a case reported in the English literature. In view of the rarity of the condition and the interesting phenomena which are associated with the mechanism of hemolysis, the case which I shall report is of more than ordinary interest.

REPORT OF CASE

History.—Mrs. A. F. (Case A 354493), an extremely pale, somewhat jaundiced, short, stout woman, aged 32 years, presented herself for examination in April, 1921. She had enjoyed unusually good health until she had suffered a moderately severe attack of influenza three and one-half years before. Convalescence had been protracted but seemed to be complete, with the exception of pallor and probably slight icterus. Nine months before, she had become definitely weaker and more anemic and dyspneic on exertion. Six months before, she had had an attack of diarrhea and vomiting. In one week, she developed marked jaundice and began to pass highly colored urine. The stools were said to have been of normal color. She improved somewhat on medical treatment at her home, but for the last few weeks she had been more anemic and more jaundiced. Her appetite had remained good, in fact her weight had gradually increased. On two or three occasions, without apparent cause, following a day or two of weakness, depression, headache and increasing jaundice, the urine had become dark for a day or two.

Examination.—The patient was obese, weighing 186 pounds, and very anemic; her skin had a lemon yellow hue. The liver and spleen did not seem to be enlarged; examination was difficult, however, because of the patient's obesity. Examination of the eyegrounds showed somewhat dilated and tortuous veins, and one or two rather large irregular hemorrhages in the periphery; not however, the type of hemorrhage usually seen in pernicious anemia. The hemoglobin was 25 per cent., the erythrocytes were 1,060,000, giving a color index of 1.1; the leukocytes were 3,800. A relative lymphocytosis was present, and an occasional normoblast. There were slight anisocytosis and poikilocytosis. The blood picture was suggestive of pernicious anemia. However, there was no glossitis; two test meals showed slight hyperacidity and the neurologic examination was entirely negative.

In the absence of characteristics of pernicious anemia the existence of hemolytic jaundice was immediately suspected, in spite of the fact that marked splenic enlargement was not present. It is to be noted also that the color index very rarely exceeded 1; subsequent counts gave the color index varying from 0.6 to 0.9.

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Examination of the duodenal contents was attempted but was unsuccessful because of lack of cooperation. The calcium time and prothrombin time were prolonged, but otherwise the various coagulation tests and the bleeding time were normal. The platelet count was 92,000. Purpura was not present. Two tests showed an increased fragility of the erythrocytes. The reading each time was 0.5 for initial hemolysis and 0.38 for complete hemolysis with control at 0.42 for initial and 0.34 for complete. The first specimen of urine examined did not show albumin or casts. Later a small amount of albumin was often present and occasionally a large amount. Casts were not found. The blood sugar was 0.12 mg. for each 100 c.c. Examinations of the stools were negative for parasites and ova. There was no indication of loss of blood.

Evidence could not be obtained that members of the family had had jaundice, splenomegaly, or diseases of the blood.

While the patient was under observation, one month after admission, a severe crisis with hemoglobinuria occurred without apparent cause. An immediate examination of the blood serum showed hemoglobinemia. A cystoscopic examination made at this time revealed bilateral hemoglobinuria with very dark chocolate-colored urine coming from both ureters. Specimens of urine from the ureters did not contain erythrocytes. Horse serum (12 c.c. serum, 6,000 units of antitoxin) seemed to check this attack of hemoglobinuria within three days.

Course.—During April, May and June, three transfusions were given. In June the patient's erythrocytes were 2,260,000, and hemoglobin was 45 per cent., the highest in the course of our observation. She maintained a fairly good condition during the summer. In August, 1921, the erythrocytes again dropped to 1,580,000 without the occurrence, however, of hemoglobinuria. The patient was very weak but had a ravenous appetite.

A thorough investigation for syphilis was made at this time with negative results. An examination of the cerebrospinal fluid was negative. A therapeutic test of five doses of neo-arsphenamin was given without apparent improvement; one of the treatments was followed by a reaction consisting of cardiac pain, dizziness, fever and syncope, which may have been partly due to the concomitant onset of hemoglobinuria. It was learned afterward that the jaundice had begun to deepen before the neo-arsphenamin was given.

The patient had four protracted attacks of hemoglobinuria while under our observation and her condition became very low with each. The onset of the attacks was with malaise, weakness, mental depression, headache and slight fever. Within a day or two the jaundice deepened and within three or four days the hemoglobinuria appeared. Although the patient had nausea and abdominal distress, she had never had an attack of gallbladder colic. During attacks she felt very ill, largely because of general prostration and headache, although she did not seem to be in serious condition. Besides these severe crises she often complained of milder attacks of nausea, weakness, headache, and a deepening jaundice without hemoglobinuria. In other words, her attacks of hemoglobinuria seemed to be superimposed on the crises of hemolytic icterus.

Treatment.—At various times, coagulen (Ciba), horse serum, ox serum, calcium by mouth, and transfusions were given in attempts to check the hemoglobinuria. In general, these agents seemed to fail in this effect, although it is possible that horse serum and ox serum may have been of some value.

During one of the patient's remissions she was given a cool bath without the development of hemoglobinuria. At one time, ice bags were placed over the loins with no deleterious effect. The patient said that she had often taken cool baths, and that being chilled from exposure had no effect in causing an attack. She did not believe that exposure or exertion in any way played a part in initiating attacks. In fact hemoglobinuria occurred while she was at absolute rest and carefully guarded from exposure in the hospital; it seemed most likely to occur after satisfactory improvement in the blood. Whenever the erythrocytes rose approximately to 2,000,000, an attack was likely to occur.

This was repeated so often that eventually the patient dreaded improvement as much as she dreaded the prostration of severe anemia for fear of another crisis with hemoglobinuria.

Résumé.—The important features of this case were (1) slight jaundice and anemia which had probably existed for three years, (2) marked jaundice and anemia of six months' duration, (3) crises similar to those of hemolytic jaundice without, however, gallbladder colic, (4) a blood picture which at times approached that of pernicious anemia, (5) the presence of bile in the stool and its absence from the urine save in crises, (6) a markedly increased fragility of the erythrocytes on two examinations, (7) an increased reticulated cell count, (8) seven severe crises which were associated with hemoglobinuria, in one of which hemoglobinemia and bilateral hemoglobinuria were demonstrated, (9) the absence of any effect of cold or exposure on the occurrence of the hemoglobinuria, (10) the absence of hemoglobinuria after transfusion, and (11) the recurrence of the hemoglobinuria when the erythrocytes reached approximately 2,000,000.

In 1900, Bettman [1] gave an excellent description of a case of hemolytic jaundice with hemoglobinuria. The attacks of hemoglobinuria occurred with some of the acholuric crises. Bettman's patient, a man, aged 29 years, first seen April 3, 1899, had been jaundiced since childhood and had had "nose bleed" occasionally for many years. There was no evidence of syphilis. The spleen was considerably enlarged; there was a definite history of crisis associated with very dark urine. Blood pigment and a few erythrocytes in the urine had been reported one year previously. Jaundice was brought on by overeating and overdrinking, by physical exertion, by emotional excitement, and especially by cool weather. Hemoglobinuria was not produced by placing the hands in ice water, although the urine contained a few erythrocytes and hemoglobinemia was demonstrated. Splenectomy was not performed and necropsy is not reported.

In 1908, Chauffard and Troisier [2] described a case of hemolytic icterus which was accompanied by attacks of hemoglobinuria. This might be regarded as a transition case between acquired hemolytic jaundice and jaundice of congenital origin, for the patient had always been pale, but had developed jaundice late in life. There was no family history of jaundice. In 1901, there had been slight jaundice; in 1902, after a fit of anger, jaundice had been marked and after that constant. In 1906, the patient had been operated on by Koch and the liver found to be normal, while the gallbladder contained thickened bile with bile sand, but no calculi. Six months later, the biliary fistula closed but jaundice persisted. Three times without chilling, and with increased jaundice, there had been an attack of fever and the urine became "malaga colored." Spectroscopic examination revealed the presence of

1. Bettman: Ueber eine besondere Form des chronischen Ikterus, München. med Wchnschr. **47**:791, 1900.

2. Chauffard, A., and Troisier, J.: Deux cas d'ictère hémolytique, Bull. et mém. Soc. méd. d. hôp. de Par. **2**:411, 1908.

hemoglobin in the urine; urobilin was abundant. Examination of the stool revealed an excess of stercobilin. The fragility of the erythrocytes was increased from 0.50 to 0.46. The reticulated cell count was increased to 12 and 14 per cent. The erythrocytes fell to 1,000,000. The spleen had been found to be slightly enlarged; the liver was not palpable.

Hijmans van den Bergh,[3] in 1911, reported a similar case, that of a man, aged 47 years. The family history was negative. The jaundice had been present for twelve years. Attacks of hemoglobinuria had occurred for six years. During the attacks the patient became very ill and anemic but had maintained a fairly satisfactory condition between times. This patient eventually developed severe anemia with high color index. The erythrocytes became reduced to 1,156,000. The stools were normal in color and there was no bile in the urine. Increased fragility of the erythrocytes was demonstrated and the reticulated cell count was high, 18 per cent. A diagnosis of hemolytic jaundice seems to be well established in spite of the fact that the spleen was not demonstrably enlarged. The patient was not followed to operation and the article contains no report of the subsequent course of the case.

Donath and Landsteiner,[4] Hoover and Stone,[5] and others have demonstrated that the hemolysis in paroxysmal hemoglobinuria is due to an autohemolysin which combines with the erythrocytes after a mixture of the patient's serum and his own or another's erythrocytes is cooled; when the mixture is warmed to body temperature, hemolysis occurs. The red corpuscles themselves are not altered (Hoover and Stone). Complement is necessary in the cooling mixture. Zinsser[6] concludes that there is considerable variation in the mechanism even in paroxysmal hemoglobinuria due to chilling.

The mechanism of hemolysis in the hemoglobinuria of hemolytic jaundice is probably quite different from that of paroxysmal hemoglobinuria due to chilling. Widal has called attention to the fact that experimental hemolysis caused by chemical poisons results in icterus if the dose is small, and in hemoglobinuria if the dose is large. It is likely that in hemolytic jaundice there is a constant destruction of

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3. Hijmans van den Bergh, A. A.: Ictère hémolytique avec crises hémoglobinuriques: fragilité globulaire, Rev. de méd. **31**:63, 1911.

4. Donath, J., and Landsteiner, K.: Weitere Beobachtungen über paroxysmale Hämoglobinurie, Centralbl. f. Bakteriol., Parasitol. u. Infekt. **45**: 204, 1908.

5. Hoover, C. F., and Stone, C. W.: Paroxysmal Hemoglobinuria, Arch. Int. Med. **2**:392 (Sept.) 1908.

6. Zinsser, H.: Infection and Resistance; an Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease, New York, Macmillan Co., 1914.

erythrocytes continuing over a period of years. This slight destruction permits the change from hemoglobin to bilirubin in a normal manner; the presence of icterus doubtless means an increase of destruction which can be partially cared for possibly by the endothelial system, but which cannot be properly eliminated by the liver; the presence of hemoglobinuria means a still greater and probably very sudden increase in hemolysis.

Pearce [7] has placed the limit of hemoglobin which may be free in the blood of the dog before hemoglobinuria occurs as 0.06 gm. for each kilogram of body weight. Sellards and Minot,[8] in 1916, in a very important piece of experimental work estimated the tolerance to the intravenous injection of hemoglobin of normal persons and of persons with the various types of anemia. Very much less hemoglobin was required to produce hemoglobinuria in hemolytic jaundice than in the anemias secondary to hemorrhage.

It may be that a renal factor is also present. Gilbert and Lereboullet,[9] in 1900, discussed the possible occurrence of a "renal form of simple acholuric icterus." Silvestri,[10] in 1921, concluded that the kidney may secrete substances which have a destructive action on erythrocytes within its vessels. An excellent summary of this viewpoint has been published by Cumston.[11] There may be, therefore, in hemolytic jaundice with hemoglobinuria a renal factor, besides sudden, severe hemolysis, which consists of either a reduction of the renal threshold or an actual hemolytic process in the kidney itself.[12]

Ashby [13] has made immunologic studies in a case of hemolytic jaundice (Case A387430) now under my observation, which in its clinical aspects is almost identical with the one herewith reported, save that hemoglobinuria has occurred only after each transfusion and not spontaneously. The patient's blood was in Group II. Ashby tested the patient's serum against his own corpuscles and against Group II corpuscles from a normal person, with and without icebox incubation.

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7. Pearce: Hemoglobinuria, Monographic Med., New York, D. Appleton and Company **1**:573, 1916.

8. Sellards, A. W., and Minot, G. R.: Injection of Hemoglobin in Man and Its Relation to Blood Destruction, with Especial Reference to the Anemias, J. M. Research **34**:469, 1916.

9. Gilbert, A., and Lereboullet, P.: La forme rénale de l'ictère acholurique simple (albuminurie intermittente, albuminurie continue, hémoglobinurie paroxystique), Bull. et mém. Soc. méd. d. hôp. de Par. **9**:662, 1901.

10. Silvestri, T.: Del fattore renale in certi casi di emoglobinuria parossistica, Policlinico **28**:1203, 1921; abstr. J. A. M. A. **77**:1291 (Oct. 15) 1921.

11. Cumston, C. G.: Clinical Notes from France. The Splenorenal Theory of Paroxysmal Hemoglobinuria, New York M. J. **110**:812, 1919.

12. Widal, M.: Discussion, Bull. et mém. Soc. méd. d. hôp. de Par. **2**:418, 1908.

13. Ashby, W. P.: Personal communication.

Tubes were incubated in the icebox for one hour, and at 37.5 C. for one and one-half hours with negative results. The dilution of serum to corpuscles was 20 to 1. The action of the serum was therefore strikingly different from that which has been reported in connection with paroxysmal hemoglobinuria.

From a study of both the clinical and the immunologic data the conclusion seems justifiable that the hemoglobinuria of hemolytic jaundice is not due to syphilis, that it is not brought on by exposure to cold, and that the mechanism of hemolysis is not analogous to that in paroxysmal hemoglobinuria due to chilling.

THE RELATION OF AGE AND OBESITY TO VITAL CAPACITY *

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In view of the frequent association of dyspnea with obesity on the one hand, and the close relationship of dyspnea with vital capacity on the other hand, it seemed of interest to learn the values of the vital capacity in obese individuals. However, with the exception of a casual mention by Myers [1] of the relation of age and obesity to the vital capacity of the lungs nothing was found in available literature.

Hutchinson,[2] in 1846, first studied the vital capacity of normal persons using the spirometer of which he was the inventor. He found that the vital capacity varied more closely with the height than any other body measurements. Until recent years the procedure has not been extensively applied to clinical medicine, but now, because of amplification and refinement of the original work of Hutchinson, it is conceded to be of some importance in diseases affecting the chest organs. Peabody and Wentworth [3] applied the test to cardiac patients and found that such patients regularly showed a decreased vital capacity when dyspneic, ranging in amount from 40 per cent. in the badly decompensated cases to nearly normal in compensated lesions.

Dreyer [4] considers vital capacity to be of great value in the assessment of physical fitness; his work has been done largely in the English Army, and the standards used by him have been mostly based on the height of the trunk taken in the sitting posture. Lundsgaard and Van Slyke,[5] and also Myers and Dreyer [6] have shown that there is a slight decrease in vital capacity in pulmonary tuberculosis, which tends to improve after treatment. It has also been determined by a number of investigators that the vital capacity is reduced in emphysema, asthma, bronchiectasis, hydrothorax and pneumonia. In cases of great physical weakness, but without diseases of either heart or lungs Peabody and

* From the Department of Laboratories and the Medical Clinic of the Buffalo General Hospital.

1. Myers, J. A.: The Value of Vital Capacity Readings in Clinical Medicine, Minnesota Med. **4**:635 (Nov.) 1921.
2. Hutchinson, J.: Med. Chir. Tr. London **29**:137, 1846.
3. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Oct.) 1917.
4. Dreyer, G.: The Assessment of Physical Fitness, New York, Paul B. Hoeber.
5. Lundsgaard, C., and Van Slyke, D. R.: J. Exper. M. **27**:65, 1918.
6. Dreyer, G., and Burrell, L. S. T.: Lancet **1**:1212 (June 5) 1920.

Sturgis [7] have found readings of only 26 per cent. below the normal. These observers also state that fatigue of the muscles of respiration produced no reduction in vital capacity in cases of heart disease.

It is clear that for a study of the vital capacity in obesity, a normal standard would be required for comparison. The normal standard in common use, however, is based on the vital capacity of persons mostly between the ages of 20 and 30 years. Obviously, the age of a maximum fitness cannot be applied as a standard for all ages. It was, therefore, decided to test the vital capacity of a series of normal persons in order to determine the required normal standard.

METHODS AND STANDARDS

The vital capacity spirometer designed by Peabody and manufactured by Sanborn and Company was used in making all of the tests. The highest of three readings were taken as the vital capacity and more than one observation was made whenever it was thought necessary.

The standards used have been those suggested by West,[8] being based both on height and surface area, the latter being estimated from the height and weight using the formula of DuBois and DuBois.[9] The vital capacity of normal persons is expressed in percentage based on surface area in Chart 1, and by both height and surface area in the tables, and the others both on surface area and height. For height, the normal standard is determined by multiplying the height in centimeters by 25 c.c. for men and 20 c.c. for women. For surface area, the standard is the product of multiplying the surface area in square meters by 2.5 liters for men and 2.0 liters for women.

DISCUSSION OF NORMALS

This group contains 184 persons varying in age from 15 to 85 years. They consist of average normal persons, who are largely of sedentary occupations, including students, physicians, nurses, hospital employees, convalescent surgical patients, and medical patients without disease of the heart or lungs and without physical weakness. The senile group was mostly obtained in homes for the aged. They were able to walk about and had only such disease as is incident with their age, e. g., arteriosclerosis, emphysema, and possibly calcification of the

7. Peabody, F. W., and Sturgis, C. C.: Clinical Studies of the Respiration. VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, Arch. Int. Med. **28**:501 (Nov.) 1921.

8. West, H. F.: Clinical Studies on the Respiration. VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

9. DuBois, D., and DuBois, E. F.: Clinical Calorimetry. Fifth Paper. The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (May) 1915.

costal cartilages. Of the 184 persons studied, 120 fell between the ages of 15 and 50. Of these, 67.5 per cent. were between 90 and 110 per cent., 25.8 per cent. were below 90, and 6.6 per cent. were above 110 per cent. with the surface area standard. Up to the age of 50 years, the average vital capacity was 95.8 per cent., then it gradually reached 50 per cent. at the age of 85 years; the greatest fall in any decade being between the ages of 50 and 60 years. Chart 1 serves to show this curve of vital capacity percentage with relation to age and may be of value in estimating the normal vital capacity, especially beyond the age of 50 years. It would seem that the standards used by West were entirely satisfactory for practical purposes up to the age of 50. The average vital capacity of this group was about 4 per cent. lower than the normal series studied by West, which may be accounted for by the

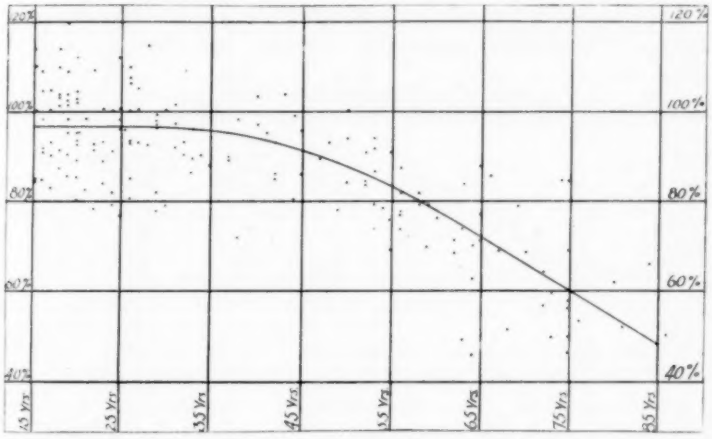

Chart 1.—Vital capacity of 184 normal patients according to age, using surface area standard.

fact that his subjects were mostly well developed men and women between the ages of 20 and 30.

There are doubtless many factors producing a reduction in vital capacity after the age of 50, but in the absence of definite disease all must be considered as manifestations of a normal aging process. They possibly constitute such conditions as loss of elasticity of the alveoli, immobility of the thorax, weakened general musculature and myocardium, and lack of exercise.

DISCUSSION OF OBESE SUBJECTS

This group comprises 32 persons who were definitely obese; twenty-seven were women and five were men. Another smaller group made

up of twenty-four people, twenty of who were women and four men, who were not definitely obese but who were distinctly "overweight," is also presented. This grouping was rather arbitrary and was based on an impression gained on physical examination. In the obese group most of the persons weighed over 80 kg. and in the "overweight" group under that figure with lower limit represented by a person who weighed 64 kg. and whose height was 152 cm. As far as could be determined, none of these people had disease of the heart or lungs, although the majority complained of some degree of dyspnea. It is interesting in this connection to note that the most pronounced case, a woman aged 33 years, weighing 198.2 kg., did not have dyspnea, and had a vital capacity by height of 87.7 per cent. and by surface area of 53 per cent. Her activities were necessarily slow and restricted, which might have been a factor.

The dyspnea that occurs in cases of obesity may be due to several factors. The frequent association of obesity with coronary sclerosis

TABLE 1.—Obese Cases in Decades

Ages	Average Vital Capacity to Height Standard, per Cent.	Average Vital Capacity to Surface Area Standard, per Cent.	Number of Cases
20-30	96.5	82.1	6
30-40	90.5	71.9	8
40-50	84.6	71.6	9
50-60	72.0	62.0	6
60-70	68.5	53.2	2

and myocarditic changes is well known. Yet, the excessive accumulation of fat in the pericardium may in itself lead to atrophic changes in the heart muscle and, consequently, to insufficiency of the latter. However, in young and especially muscular persons, it may require a long time for such secondary changes to be brought about, during which time the obese subject may enjoy good health as far as his cardiorespiratory apparatus is concerned.

Between the ages of 20 and 30, only six obese persons were studied. Of these, four were under 100 per cent. by the height standard and all by the surface area standard. In this group (Table 1), the vital capacity was essentially normal by the height standard between the ages of 20 and 30, dropping slowly to the age of 50, where there was a rather sudden reduction of 12 per cent., behaving about as normal persons do. Only two subjects had a vital capacity above 100 per cent. by the height standard. The vital capacity according to surface area was considerably reduced, as would be expected, there being an average difference from the height standard of 14.3 per cent. Although the curve of reduction according to age follows much the same course as

in the case of normal people, there was a tendency for the vital capacity of obese individuals to be reduced even by the height standard. However, between the ages of 15 and 50 the average vital capacity in the normal group was 95.8 per cent., and in the combined obese and "overweight" groups, 75.8 per cent. by the surface area standard and 88.8 per cent. by the height standard. In estimating the vital capacity of obese and "overweight" people it is probably better to use the height standard or make a correction by adding 20 per cent. to the surface area standard; this being the difference between the normal vital capacity and that of the obese and "overweight" groups.

Chart 2 represents the vital capacities of the obese and "overweight" groups for all ages, in order of weight, beginning with the heaviest. The (.) indicates the percentage according to height and the (x)

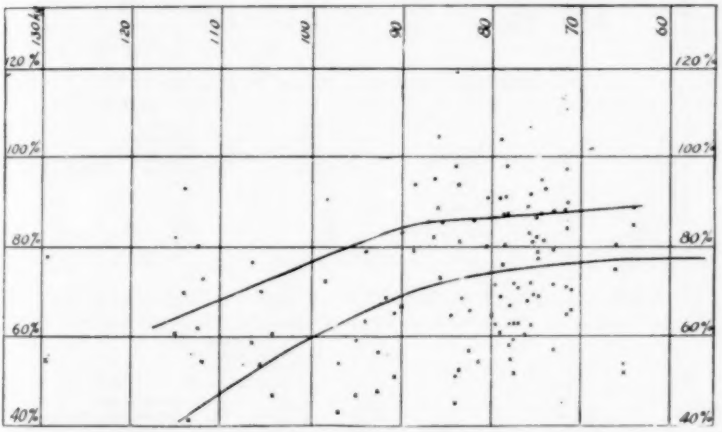

Chart 2.—Vital capacity of obese class beginning with heaviest. • = per cent. height; × = per cent. surface area.

according to surface area. It will be seen that there is a slight tendency for the vital capacity to increase as the weight decreases.

In Table 2, six obese cases are grouped separately from the normal obese group, because of the diagnosis of "chronic myocarditis." All had symptoms of a cardiac nature of from 3 to 15 years' duration—dyspnea, palpitation and easy fatigue—and all had a slight vascular hypertension. None of this group was decompensated and but one had slight edema. The vital capacities of all were between 50 and 60 per cent. by the height standard and 40 and 50 per cent. by that based on surface area. A corresponding group of cardiac patients would not, judging from the work of Peabody, have shown this degree of reduction. However, if the correction of 20 per cent. be added to the surface

area percentage, the result would be about what one would expect in such cases.

One patient, a girl, aged 18, who had acromegaly, and who weighed 90 kg., most of the increase having taken place in the past two years, had a vital capacity of 130.5 per cent. by height and 109.4 per cent. by surface area. This case was not included in the obese group as she was considered as being distinctly pathologic. This, by the way,

TABLE 2.—Obese Cardiac Cases

Age	Sex	Weight, Kg.	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity to Height Standard, per Cent.	Vital Capacity to Surface Area Standard, per Cent.
51	F	97.0	157.0	1.96	1,700	54	43
45	F	94.9	156.5	1.94	1,850	59	47
45	F	77.8	154.5	1.77	1,820	59	52
45	F	85.0	164.0	1.92	1,700	52	44
43	F	92.4	158.0	1.89	1,800	57	48
42	F	113.3	164.5	2.21	1,850	56	42

TABLE 3.—Overweight Cases in Decades

Ages	Average Vital Capacity to Height Standard, per Cent.	Average Vital Capacity to Surface Area Standard, per Cent.	Number of Cases
20-30	84.5	77.0	6
30-40	83.8	76.9	4
40-50	88.6	75.5	7
50-60	76.2	68.3	7

TABLE 4.—Effect of Weight Reduction on Vital Capacity

Case	Date	Weight, Kg.	Age	Vital Capacity in C.c.	Percentage Height Standard	Percentage Surface Area Standard	Remarks
E. F.	12/21/21	84.7	31	3,730	115.1	98.0	No dyspnea
	4/20/22	74.5	..	3,800	117.2	106.1	General improvement
R. C.	6/ 8/21	78.5	29	3,000	91.0	80.0	Dyspnea +
	4/22/22	67.2	..	3,000	91.0	87.8	Dyspnea absent
C. S.	9/23/21	114.9	30	2,700	82.2	61.9	Dyspnea +
	4/21/22	100.1	..	3,600	109.7	87.3	Dyspnea absent; general improvement
M. K.	2/20/22	73.6	50	2,300	75.6	67.2	Diabetes, dyspnea +
	4/19/22	62.5	..	2,600	85.5	81.7	Dyspnea not noticeable; general improvement

may, perhaps, be accounted for by the actual increase in the bony framework of the thorax, as such cases sometimes show.

Table 3 shows twenty-four cases arranged in decades; the subjects were not considered obese but were "overweight." Like the other groups of normal and obese subjects, the vital capacity makes a rather precipitant drop after the age of 50 years, averaging 12 per cent. The average vital capacity is similar to the obese group, being reduced by the surface area standard and only slightly so by the height standard.

Table 4 shows a study of four patients, two obese and two "overweight." Their weights were reduced by dietary measures for the

TABLE 5.—NORMALS

Age	Sex	Weight, Kg.	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
15	♀	47.1	164.0	1.49	3,000	91.4	100.6
15	♂	58.6	169.0	1.69	4,600	109.0	110.3
15	♂	52.2	157.0	1.51	4,300	109.6	114.0
15	♀	36.6	155.0	1.28	2,700	69.7	84.3
15	♀	63.0	173.0	1.75	3,700	85.6	84.6
16	♀	54.0	156.0	1.52	3,750	96.1	98.6
16	♀	60.0	161.0	1.63	3,700	92.0	90.9
16	♀	55.0	161.0	1.57	4,100	101.9	104.5
16	♀	51.3	157.0	1.49	3,150	80.3	84.7
16	♀	58.8	166.0	1.65	4,500	108.4	109.2
16	♂	65.0	163.0	1.70	3,900	95.8	91.7
17	♀	58.6	158.0	1.59	3,300	83.5	83.1
17	♀	55.6	173.0	1.64	3,700	85.6	90.2
17	♀	60.2	167.0	1.68	4,400	108.4	104.7
17	♀	41.1	144.0	1.27	2,550	88.8	100.3
17	♀	55.5	160.5	1.55	2,950	92.0	93.6
18	♀	48.3	160.0	1.47	2,700	84.3	91.5
18	♀	52.7	161.2	1.54	3,200	99.0	103 8
18	♀	57.0	163.0	1.61	3,700	114.0	110 0
18	♂	82.5	173.0	1.97	5,000	115.7	101.6
18	♂	54.0	170.0	1.62	4,200	98.8	103.7
18	♂	61.3	166.0	1.68	4,800	115.6	114.2
19	♂	57.2	160.0	1.59	3,400	85.0	85.6
19	♀	49.5	158.7	1.48	3,050	96.2	103.8
19	♀	49.7	155.4	1.46	3,000	96.4	102.3
19	♀	55.0	157.9	1.55	3,050	96.5	98.3
19	♀	71.8	168.9	1.82	4,400	130.1	120.8
19	♀	61.8	168.1	1.70	3,700	110.1	108.8
19	♀	56.1	166.3	1.62	3,100	93.0	95.3
19	♀	58.6	161.2	1.62	3,300	102.4	101.8
19	♀	57.2	154.1	1.55	2,800	90.9	90.3
20	♂	61.3	165.0	1.67	4,700	114.0	112.4
20	♀	46.3	151.1	1.39	2,900	96.0	104.4
20	♀	72.5	159.2	1.75	2,800	88.0	80.0
20	♀	63.6	161.8	1.68	3,200	98.7	95.2
20	♀	62.9	154.9	1.62	3,000	96.7	92.5
20	♀	52.2	158.7	1.52	2,700	85.1	88.8
20	♀	56.8	162.5	1.60	3,000	92.3	93.7
20	♀	58.5	156.5	1.58	2,700	86.0	85.0
20	♀	46.0	158.5	1.43	2,960	93.0	103.0
20	♀	41.3	146.0	1.29	2,450	84.0	95.0
20	♀	50.5	161.5	1.51	3,100	96.0	102.0
21	♀	60.4	160.0	1.63	2,700	84.3	82.8
21	♂	66.5	182.5	1.87	4,600	100.8	98.5
22	♀	64.3	157.9	1.65	2,600	82.2	78.5
22	♀	66.3	155.4	1.66	3,050	98.0	91.8
22	♀	44.7	158.0	1.37	3,000	98.0	109.0
22	♂	82.1	178.5	2.01	4,650	104.2	92.6
23	♀	63.0	163.5	1.68	3,000	91.7	89.2
23	♀	46.5	158.5	1.43	2,400	76.0	84.0
23	♀	50.6	171.5	1.56	2,900	85.0	93.0
23	♂	61.6	166.0	1.68	4,220	101.6	100.4
24	♀	57.2	166.3	1.64	2,600	78.3	79.2
24	♀	77.2	164.3	1.84	3,020	91.1	82.0
24	♀	47.2	157.5	1.43	2,600	82.4	91.0
24	♂	61.4	176.5	1.76	4,400	99.7	100 0
25	♀	52.0	169.0	1.57	3,000	89.0	96.0
25	♀	55.4	158.5	1.56	2,400	75.7	76.9
25	♀	47.6	158.5	1.45	2,830	89.0	98.0
25	♂	65.0	168.5	1.71	4,300	105.1	100.7
25	♀	45.7	158.0	1.43	2,750	87.0	96.0
25	♀	54.3	166.5	1.60	3,600	108.1	112.5
26	♀	51.8	157.4	1.50	2,800	88.8	93.3
26	♀	68.4	162.0	1.73	3,220	99.3	93.0
26	♀	61.9	167.0	1.70	2,900	86.8	85.2
26	♀	61.3	163.0	1.64	3,300	101.0	100.3
26	♂	80.0	173.0	1.99	5,500	127.0	110.0
26	♂	48.6	170.0	1.54	2,100	73.0	81.0
26	♂	63.0	174.0	1.76	4,700	108.0	106 8
26	♀	44.5	161.5	1.42	3,000	93.0	106.0
27	♂	84.1	180.0	2.04	5,125	113.9	109.4
27	♂	68.2	173.0	1.81	4,200	97.0	93.0
27	♀	54.4	169.0	1.62	3,400	100.5	104.9
28	♀	54.2	163.5	1.58	3,600	110.0	114.0
28	♀	55.0	161.8	1.57	3,600	111.1	114.2

TABLE 5.—NORMALS—(*Continued*)

Age	Sex	Weight, Kg.	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
28	♂	56.7	156.0	1.56	2,900	92.9	92.9
29	♂	49.5	164.5	1.52	2,950	89.6	97.0
29	♂	69.0	164.5	1.75	3,400	103.0	97.1
29	♂	71.0	172.0	1.84	4,500	104.6	97.8
29	♂	41.5	151.5	1.31	2,050	67.6	78.2
29	♂	75.5	180.0	1.95	4,000	88.8	81.9
29	♂	67.5	148.0	1.61	3,200	108.0	99.3
30	♂	41.9	161.0	1.40	2,800	86.9	100.0
30	♂	60.7	173.0	1.73	3,400	79.0	79.0
31	♂	53.6	165.1	1.57	3,200	96.9	101.5
31	♂	66.5	166.0	1.74	3,200	96.3	91.9
31	♂	72.0	179.5	1.91	4,650	103.8	97.4
32	♂	71.2	168.5	1.81	4,900	116.3	108 4
32	♂	40.6	160.5	1.38	3,200	80.0	96.0
32	♂	66.6	167.0	1.75	3,450	103.2	90.8
32	♂	42.1	161.5	1.40	3,250	100.0	116.0
33	♂	62.0	157.5	1.63	3,650	92.6	89.6
33	♂	66.5	181.0	1.85	4,000	88.5	86.5
33	♂	56.3	164.3	1.61	3,100	94.2	96.2
34	♂	54.2	153.0	1.50	2,700	88.2	90.0
35	♂	53.5	160.5	1.53	2,700	84.0	88 0
35	♂	42.7	153.0	1.36	3,000	98.0	110.2
36	♂	47.5	159.0	1.46	3,100	97.4	106.1
36	♂	56.4	157.5	1.57	3,000	95.2	95.5
37	♂	69.8	173.0	1.83	4,100	94.9	89.7
37	♂	74.2	173.5	1.88	4,200	96.7	89.3
38	♂	45.9	151.5	1.39	2,200	72.6	74.0
38	♂	51.4	154.5	1.47	2,900	93.8	98.6
38	♂	67.9	186.5	1.91	4,500	96.5	94 3
40	♂	58.1	184.0	1.77	4,300	94.0	97.0
40	♂	74.2	167.5	1.83	3,200	95.5	87.5
40	♂	62.7	172.0	1.74	3,600	104.6	103.4
41	♂	51.8	159.5	1.51	2,300	72.0	76.0
41	♂	45.2	157.5	1.42	2,700	85.7	95.0
42	♂	64.2	154.5	1.63	3,050	98.7	93.5
42	♂	66.1	158.5	1.67	2,900	91.0	86.0
42	♂	75.2	165.5	1.82	3,100	93.6	85.1
43	♂	67.0	165.5	1.74	4,500	108.6	103.4
44	♂	48.9	151.5	1.43	2,800	92.4	98.1
44	♂	70.0	171.0	1.82	3,800	91.3	80.3
45	♂	49.3	159.0	1.48	2,550	80.1	86.9
45	♂	49.8	162.5	1.51	2,900	89.2	96.0
47	♂	52.4	159.0	1.52	2,700	85.0	89.0
48	♂	48.5	163 5	1.50	2,700	83.5	90 3
49	♂	53.5	154.0	1.50	2,350	76.2	78.3
50	♂	54.3	149.5	1.48	2,800	93.6	94.5
50	♂	64.2	163.0	1.69	3,550	87.0	84.0
50	♂	61.4	160.0	1.64	3,300	103.0	100.6
52	♂	66.8	175.0	1.81	4,100	94.0	91.0
52	♂	73.0	171.0	1.85	3,900	91.3	84.4
52	♂	78.0	168.0	1.86	3,900	92.8	83.8
53	♂	68.5	176.0	1.78	4,200	95.4	94.3
53	♂	63.8	152.0	1.61	2,800	92.1	86.9
53	♂	60.4	153.5	1.58	2,500	81.4	79.0
53	♂	70.0	174.0	1.84	4,400	101.1	91.6
53	♂	38.9	161.0	1.35	2,000	62.1	74.0
54	♂	50.2	155.5	1.46	2,300	73.9	78.7
54	♂	78.3	155.0	1.77	2,500	64.6	56.5
55	♂	64.8	168.5	1.74	3,000	71.2	68.9
55	♂	62.0	163.0	1.67	3,800	96.3	91.1
55	♂	63.3	170.0	1.73	3,300	77.6	76.0
56	♂	73.0	164.0	1.79	3,500	85.3	78.3
56	♂	61.2	158.0	1.62	2,400	75.9	74.0
56	♂	69.1	166.5	1.77	3,100	93.0	87.5
56	♂	54.7	171.5	1.76	3,400	79.2	77.2
57	♂	55.9	143.0	1.45	2,100	73.4	72.4
58	♂	66.9	160.0	1.70	2,700	84.3	79.4
58	♂	74.0	164.0	1.80	3,700	90.2	82.2
59	♂	46.3	151.0	1.39	2,200	72.8	79.1
59	♂	58.0	157.0	1.58	2,200	70.0	69.6
60	♂	43.6	163.0	1.43	2,200	67.4	76.9
62	♂	41.5	162.5	1.40	2,000	61.5	71.4
62	♀	54.5	162.0	1.60	2,200	67.9	68.7

TABLE 5.—NORMALS—(*Continued*)

Age	Sex	Weight, Kg.	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
63	♂	58.6	161.0	1.61	3,400	84.5	84.1
63	♂	80.0	173.0	1.94	3,600	83.3	74.2
63	♀	52.8	157.5	1.51	1,500	47.6	49.6
64	♂	57.0	167.0	1.57	1,800	43.1	45.9
64	♀	61.3	162.0	1.65	2,100	61.7	63.1
64	♂	58.1	173.5	1.71	3,000	69.1	70.2
65	♂	76.6	170.0	1.88	4,150	97.6	88.3
65	♀	59.4	150.5	1.54	2,200	73.0	71.4
66	♂	63.1	164.0	1.68	3,600	87.8	85.7
67	♂	52.0	166.0	1.56	3,950	95.1	101.2
68	♂	77.7	159.0	1.80	2,350	59.1	52.2
69	♂	72.0	167.0	1.80	3,600	86.0	79.0
70	♂	76.0	177.5	1.94	4,300	96.8	88.6
70	♂	57.2	157.0	1.56	2,800	71.4	71.8
70	♀	57.7	146.5	1.50	1,700	58.0	56.6
71	♂	54.0	164.0	1.58	2,900	70.7	73.4
72	♀	55.5	149.5	1.49	1,700	56.8	57.0
72	♂	68.1	161.0	1.72	1,300	32.3	30.2
72	♀	70.4	156.5	1.71	2,200	70.2	64.0
73	♂	81.0	170.0	1.98	2,400	56.4	49.8
73	♂	65.0	161.0	1.68	2,500	62.1	59.3
74	♀	41.1	157.0	1.36	2,300	73.2	84.5
75	♀	57.3	157.0	1.57	2,150	68.4	68.4
75	♀	47.2	150.0	1.40	1,300	43.3	46.4
75	♂	61.3	169.0	1.70	3,600	85.3	84.5
75	♂	69.0	170.0	1.8	2,600	61.1	57.7
75	♂	68.6	157.0	1.7	2,100	53.5	49.4
76	♀	56.8	160.0	1.58	1,700	53.1	53.8
79	♂	75.0	171.0	1.87	2,900	67.9	62.0
81	♂	73.1	163.0	1.79	2,350	57.7	52.5
82	♀	41.5	155.0	1.35	1,000	32.2	37.0
84	♂	58.1	160.0	1.60	2,650	66.0	66.0
84	♀	64.5	154.0	1.62	1,100	35.7	33.8
85	♀	51.3	149.5	1.44	1,400	46.8	48.6
86	♀	35.4	141.0	1.18	1,200	42.5	50.8
94	♀	56.8	158.5	1.57	2,200	69.4	70.0

TABLE 6.—OVERWEIGHTS

Age	Sex	Weight, Kg.	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
48	♂	96.6	175.0	2.12	4,100	90.0	77.0
45	♂	89.0	172.0	2.03	5,000	116.2	98.6
48	♀	79.8	156.5	1.80	2,250	71.8	62.5
56	♀	79.0	158.0	1.80	2,200	69.6	60.9
60	♀	78.8	171.0	1.91	2,900	85.0	76.0
53	♀	78.8	164.0	1.86	3,225	98.0	87.0
29	♀	78.5	164.0	1.85	3,000	91.0	80.0
41	♀	78.0	158.5	1.80	2,000	63.0	55.5
39	♂	77.0	163.5	1.83	2,900	71.0	63.0
59	♀	76.3	153.5	1.74	2,100	68.0	60.0
24	♀	75.7	165.0	1.83	3,020	92.0	83.0
42	♀	75.5	157.7	1.77	2,550	80.8	72.0
51	♀	75.5	165.5	1.83	2,300	69.4	62.8
33	♀	75.2	159.5	1.67	2,750	86.8	82.0
21	♀	73.8	156.0	1.74	2,750	88.1	79.0
52	♀	73.6	152.0	1.71	2,300	75.8	67.2
38	♀	71.7	154.0	1.71	3,000	97.0	87.7
54	♀	71.6	162.0	1.76	2,300	70.9	65.3
23	♀	71.5	152.0	1.68	2,800	92.1	83.3
58	♂	71.2	159.5	1.74	2,900	72.6	66.6
40	♀	66.1	152.0	1.63	2,450	80.5	75.1
29	♀	64.7	157.0	1.64	1,700	54.0	52.0
21	♀	64.0	157.6	1.65	2,800	88.8	84.8

purpose of observing the effect on symptoms and vital capacity. The reduction in all exceeded 10 kg. and was brought about in periods, varying from two to ten months. Dyspnea was present in three, and general symptoms, easy fatigue, lassitude and a "heavy feeling" was complained of by all. The vital capacity was above 100 per cent. in but one case, the subject being the only one of the four who did not have dyspnea. These symptoms improved or disappeared in all coincident with the loss of weight. The vital capacity in cubic centimeters increased in two cases, but remained constant in the others. In one

TABLE 7.—OBESITIES

Age	Sex	Weight, Kg	Height, Cm.	Surface Area Square Meters	Vital Capacity C.c.	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
33	♀	198.2	171.0	2.82	3,000	87.7	53.0
34	♀	129.5	153.0	2.18	2,400	78.0	55.0
20	♀	114.9	164.5	2.17	2,700	82.2	61.9
33	♀	114.0	162.0	2.15	3,000	93.0	70.0
53	♂	112.3	169.5	2.20	3,400	80.0	62.0
50	♂	112.2	159.0	2.10	2,900	73.0	55.1
63	♀	106.66	164.0	2.12	2,500	76.6	59.0
42	♀	105.9	157.5	2.04	2,200	70.0	54.0
63	♂	104.4	165.0	2.11	2,500	60.6	47.4
40	♀	98.2	159.0	2.00	2,900	91.0	72.5
42	♀	94.1	154.0	1.92	2,450	79.5	63.8
45	♀	91.7	162.2	1.97	2,700	83.0	68.5
21	♀	88.8	164.5	1.96	3,100	94.2	79.0
42	♂	87.2	164.0	1.94	3,500	85.3	72.1
47	♀	86.8	173.5	2.02	3,300	95.0	82.0
26	♀	86.4	159.0	1.89	3,350	105.0	89.0
48	♀	86.0	168.0	1.96	2,850	84.8	72.7
54	♂	84.7	166.5	1.94	2,600	62.5	53.5
31	♀	84.7	162.0	1.90	3,730	115.0	98.0
32	♀	83.9	158.0	1.85	3,000	94.3	81.0
50	♀	83.3	158.0	1.85	2,100	66.4	56.7
55	♀	82.4	163.0	1.88	2,100	64.0	55.0
22	♀	82.2	153.0	1.79	2,600	84.9	72.6
35	♀	80.6	165.5	1.88	3,000	91.0	80.0
52	♀	80.0	156.0	1.80	2,300	74.0	64.0
26	♀	79.4	156.0	1.79	3,250	104.0	90.7
52	♀	78.3	148.5	1.71	2,000	67.0	58.0
34	♀	77.1	152.5	1.74	2,200	72.1	63.2
50	♀	77.0	153.0	1.74	2,700	88.2	77.5
40	♀	74.2	167.5	1.83	3,200	95.5	87.5
43	♀	74.8	154.5	1.74	2,400	77.6	68.9
23	♀	73.9	150.5	1.68	2,800	93.0	83.0

of these the increase was 27.5 per cent. by height. While this is interesting, it is not consistent with the findings in the other cases. However, in these four cases, after the weight reduction there was an increase in the vital capacity by surface area, bringing it nearly to normal. This study would indicate that the tendency to dyspnea which is common in people who are overweight is possibly, in part, accounted for by a reduction in vital capacity. Presumably, it is wise to reduce the weight of overweight persons slowly, if they complain of symptoms suggesting cardiac embarrassment. This is especially so if their vital capacity shows a definite reduction.

CONCLUSION

This study seems to warrant the following deductions:

1. Using standards based on persons between the ages of 20 and 30, the vital capacity is within normal limits up to the age of 50, thereafter the fall is gradual, reaching 50 per cent. at the age of 85. The greatest drop is between the ages of 50 and 60.

2. The vital capacity of obese and "overweight" people is but slightly less than normal, using the height standard, but averages 20 per cent. less by surface area, up to the age of 50.

3. The height standard, or the addition of 20 per cent. to the result obtained by using the surface area standard may be used in estimating the vital capacity of obese or "overweight" subjects.

4. The tendency to dyspnea, which is often present in people who are much overweight, may be accounted for, in part, by a reduction of the vital capacity.

5. It appears advisable to reduce the weight of obese people slowly, if there are annoying symptoms of a cardiac nature. This is especially so if the vital capacity shows a definite reduction.

ACID-BASE EQUILIBRIUM

I. CLINICAL STUDIES IN ALKALOSIS *

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Although the practical aspects of the acid-base equilibrium problem are appreciated by the clinician, the observations and discussions have been limited to a large degree to those cases in which the equilibrium has been shifted toward the acid side. Observations reported in the last few years and our own studies indicate that an alkalotic condition of the body is perhaps as important clinically, if not more so, than an acidotic condition. In an acidosis resulting from the ingestion of fixed acids, from the retention of carbon dioxid, from deficient oxidation with the resulting accumulation of acid metabolites, or by acid retention due to renal involvement, there is at first an increased lung ventilation, but only after a decided acidosis of p_H 7.1—7.0 is there a marked disturbance of the normal physiological functions characterized by unsteadiness of motion, stupor and a coma, usually passing into death.

In order to clarify the discussion it is well to recall the possible variations in the acid-base balance as presented recently by various writers in a greatly clarified manner. The fundamental conception which displaced the chaos and confusion of this problem with a practical working knowledge was set forth by Hasselbach.[1] He showed that in blood there was a definite relationship among three interdependent variables, $NaHCO_3$, CO_2 and p_H, so that the determination of any two would give the third.

$$p_H = K \frac{H_2CO_3}{NaHCO_3}$$

When the reaction of the blood is normal, $p_H = 7.4$, the ratio of H_2CO_3 to $NaHCO_3$ is as 1 is to 20 or

$$\frac{0.00155 \text{ mol per liter } H_2CO_3}{0.0310 \text{ mol per liter } NaHCO_3} = \frac{1}{20} \text{ equiv. to } p_H = 7.4$$

The mathematical relationship Hasselbach gave as follows:

$$p_H = pK_1 + \log \frac{NaHCO_3}{H_2CO_3}$$

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* From the Laboratory of Physiological Chemistry, University of Wisconsin.

1. Hasselbalch, K. A.: Die "reduzierte" und die "regulierte" Wasserstoffzahl des Blutes, Biochem. Ztschr. **74**:56, 1916.

The value of pK_1 was shown by Haggard and Henderson [2] to be 6.10. An example for normal blood would be:

$$6.10 + \log \frac{50 \text{ (vol. \% } CO_2 \text{ as } NaHCO_3)}{2.5 \text{ (vol. \% } CO_2 \text{ as } H_2CO_3} = p_H = 7.4$$

However, it has been more recently shown by L. J. Henderson [3] that the above interdependence of the three variables, p_H, $NaHCO_3$ and H_2CO_3 extends also to three more important simultaneous variables, namely free oxygen (HbO_2) and the chlorid content of the plasma (PCl). This may also be presented as follows:

$$\frac{H_2CO_3}{NaHCO_3} = K \frac{O_2}{HbO_2} = K \frac{p_H}{PCl}$$

The above conception is indeed a very helpful simplification of the heretofore indefinite notions of the relation of the blood buffers. It is also altogether probable that this interdependence applies not only to the respiratory variables but that a mathematical expression can be formulated including all the buffer systems of the blood, as for example:

$$p_H = K \frac{NH_2PO_4}{N_2HPO_4} = K \frac{\text{Acid Proteinate}}{\text{Protein}} = K \frac{\text{Protein}}{\text{Na Proteinate}} \text{ etc.}$$

It is, therefore, apparent that in clinical studies we are only concerned with the determination of two variables in order to define our systems. Up to the present time these variables have been either p_H and $NaHCO_3$ or H_2CO_3 as CO_2 tension and $NaHCO_3$. D. D. Van Slyke [4] has given a very clear presentation based on the above three variables of the possible variations in acid-base balance. He sets forth nine possible conditions, all of which may occur clinically: The bicarbonate may be high, low or normal and in each condition the p_H may be high, low or normal. A helpful terminology has been introduced in which abnormal bicarbonate variations with a normal p_H are spoken of as compensated and bicarbonate variations with abnormal p_H as uncompensated alkalosis or acidosis. There thus occurs a condition of compensated alkali or carbon dioxid excess, which condition may pass either to uncompensated alkali excess with a high p_H, 7.5-7.8, or to uncompensated carbon dioxid excess with a low p_H, 7.3-7.0. Similarly a compensated alkali or carbon dioxid

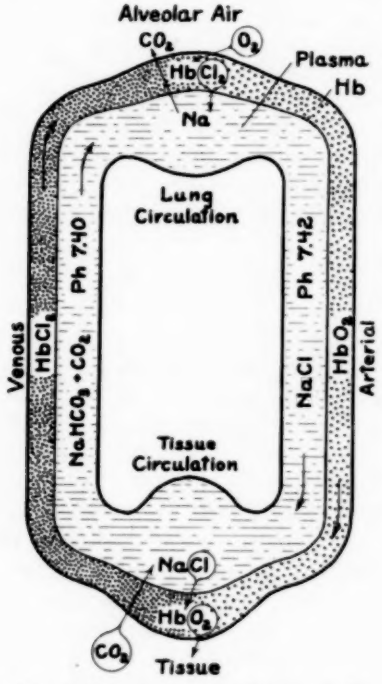
2. Haggard, W. H., and Henderson, Y.: Hematorespiratory Functions, J. Biol. Chem. **39**:163, 1919.

3. Henderson, L. J.: Blood as a Physicochemical System, J. Biol. Chem. **46**:411, 1921.

4. Van Slyke, D. D.: Studies of Acidosis, XVII. The Normal and Abnormal Variations in the Acid-Base Balance of the Blood, J. Biol. Chem. **48**:153, 1921.

deficit may pass either to uncompensated alkali deficit with a p_H of 7.3-7.0 or to uncompensated carbon dioxid deficit with a p_H of 7.5-7.8.

In order to understand the relationship of the changes within the blood to the acid-base balance and oxygen exchange of the body, it will be necessary to consider more closely the changes that occur in the variables p_H, $NaHCO_3$, H_2CO_3, O_2, HbO_2 and plasma chlorid as represented by the L. Henderson[4] nomogram during the normal circulation of the blood. These changes can best be understood from a study of the diagram. This diagram shows in a qualitative way the



Blood changes in a respiratory cycle.

blood changes in a respiratory cycle. The top portion represents the lung capillary circulation and the bottom portion represents the tissue circulation. The whole blood represented by the enclosed system is divided diagramatically into plasma and red corpuscles or hemoglobin, thus making it possible to indicate the changes that take place between them. A convenient place to start to follow the changes indicated in the cycle is in the tissue capillary circulation. The carbon dioxid produced in the tissues passes to the plasma, where the carbon dioxid

tension is lower. The dissociation of the sodium chlorid renders the sodium ion available for the formation of sodium bicarbonate with the carbon dioxid. The passage of the chlorin ion to the HbO_2, together with the change in oxygen tension, is instrumental in the passage of the oxygen to the tissues, leaving HbCl. The venous blood now carries a large amount of H_2CO_3 and $NaHCO_3$ in such a ratio that it has but a slightly lower p_H than that of arterial blood. The hemoglobin, which has been instrumental in carrying oxygen, is now returned as the chlorid. When the venous blood reaches the pulmonary circulation the reverse processes take place. The carbon dioxid is given up to the lower gaseous tension of the alveolar air, thus liberating the sodium. This would, however, leave the plasma too alkaline, so the chlorin passes from the hemoglobin to the plasma to again form sodium chlorid. This change, together with reversed change in oxygen tension, enables the oxygen to pass from the alveoli to the hemoglobin. The arterial blood then carries HbO_2 and the chlorin as sodium chlorid ready to repeat the cycle. It must, however, be remembered that this is merely a schematic representation of a few of the variables of a very complex system and that the reason for the changes and their exact mechanism of action is very imperfectly understood.

Two methods have been used for accurate determinations of acid-base variations in whole blood. In this laboratory we use the gas chain method for determining the p_H and the Van Slyke apparatus for determining the total carbon dioxid. Haggard and Henderson [2] have introduced a method by means of which the p_H can be measured indirectly by equilibrating blood with various known carbon dioxid tensions and then determining the combined carbon dioxid for each tension. In this way, by plotting the total carbon dioxid against carbon dioxid tension a p_H line is determined. The practicability of this method is as yet questionable, inasmuch as it introduces a third variable—a change of the oxygen tension of the blood. The exact effect of this is as yet not clear.

CLINICAL ALKALOSIS

Clinically alkalosis falls either into alkali excess or carbon dioxid deficit. In either case the p_H is above normal and is usually within the limits of p_H 7.5-7.8. Alkali excess is usually the result of excessive administration of sodium bicarbonate either by mouth or intravenously.[5]

5. Howland, J., and Marriott, W. McK.: Observations on the Calcium Content of the Blood in Infantile Tetany and on the Effect of Treatment by Calcium, Quart. J. M. **11**:289, 1917.

We have observed it as the result of prolonged administration of sodium citrate, sodium acetate and sodium bicarbonate, together with sodium salicylate in rheumatic fever. Alkali excess also obtains in loss of hydrochloric acid from the stomach in pernicious vomiting or in pyloric obstruction with subsequent vomiting or washing out the stomach for several days with a stomach pump.[6]

In uncompensated carbon dioxid deficit the p_H is above the normal limits, thus designating an alkalosis, although there really is a marked diminution in blood and body alkali. This reduction of alkali is the result of a tendency of the body to reduce the alkali to such a level that it will compensate the low carbon dioxid level. This condition can be caused by voluntary hyperpnea.[7] It also obtains in anoxemic dyspnea either as a result of decreased oxygen supply[8] or in failure of the blood to carry oxygen as in the early hours of carbon monoxid poisoning.[9] It has also been shown to exist in the elevation of body temperature by immersion in warm water.[10]

The effects of either alkali excess or carbon dioxid deficit to a large extent are the same. Unless there is an accompanying renal involvement, the urine tends to become alkaline owing to elimination of alkali. In alkali excess the bicarbonate elimination is very much greater, often several grams per hour, than in carbon dioxid deficit where the excretion usually is only a fraction of a gram per hour.[11] In either case there is a diminution of titratable acids with a comparable decrease or even complete absence of ammonia. The elimination of acetone bodies has also been noted under both conditions.[11] A point of difference however, is the increase in alveolar carbon dioxid in alkali excess and a decrease in carbon dioxid deficit.

The outstanding clinical symptoms of a marked alkalosis of either type have been well described by various writers as the characteristic

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6. MacCallum, W. A., Luntz, J., Vermilye, H. N., Leggett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins, Hosp. **31**:1, 1920.

7. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnea on the Carbon Dioxide Combining Power of the Plasma, the Carbon Dioxide Tension of Alveolar Air, and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, Am. J. Physiol. **51**:568, 1920.

8. Haggard, W. H., and Henderson, Y.: Hematorespiratory Functions: The Fallacy of Asphyxial Acidosis, J. Biol. Chem. **43**:3, 1920.

9. Haggard, W. H., and Henderson, Y.: Hematorespiratory Functions: Respiratory and Blood Alkali during Carbon Monoxid Asphyxia, J. Biol. Chem. **47**:421, 1921.

10. Haggard, W. H., Bazett, H. C., and Haldane, J. B. S.: Hematorespiratory Functions: The Alteration of the Carbon Dioxid Ratio in the Blood during Elevation of Body Temperature, J. Biol. Chem. **44**:131, 1920. Some Effects of Hot Baths on Man, J. Physiol. **55**, IV, 1921.

11. Davies, H. W., Haldane, J. B. S., and Kennaway, E. L.: Experiments on the Regulation of the Blood's Alkalinity, J. Physiol. **54**:32, 1920.

development of tetany and, finally, convulsions.[6, 12] The various steps in the development of tetany are best seen in marked voluntary hyperpnea. The picture is practically identical with that seen at the bedside in severe alkalosis. There is at first noted a numbness of the extremities especially the fingers. This is followed by a tingling of the fingers, quivering of the eyelids and a tenseness of the facial muscles. The fingers become flexed at the metacarpophalangeal joints in a characteristic manner and may suddenly go into a marked spasm. The facial muscles go into a decided quiver with most marked contraction of the orbicularis oris, risorius and triangularis muscles, giving rise to a peculiar grinning expression and difficulty of articulation. Tapping a branch of the facial nerve, Chvostek's sign for tetany, results in spasmodic contraction of the facial muscles.

Erb's sign of increased electrical irritability of the muscles of the forearm is apparently a constant accompaniment of a high blood p_H. Trousseau's sign is also of diagnostic value in the determination of the onset of the tetany of alkalosis.

As to the causative relation of alkalosis to tetany little is known beyond a few general observations. Biederman [13] showed that the excitability of isolated voluntary muscle was greatly heightened by increasing, up to a certain limit, the alkalinity of the solution in which it was immersed. Dale and Thacker [14] demonstrated decreased duration of the sino-auricular interval, the auriculoventricular interval and the cardiac cycle with increase in hydroxyl ions in perfusion of the frog's heart. McClendon obtained similar results in studying the effect of reaction on the pulsation rate of the hearts of the jelly fish and conch. That alkalotic tetany is the result of change in the muscle or myoneural junction rather than in the nerve fiber proper may be interpreted from the work of Adrian [15] who demonstrated the disappearance of the supernormal phase of a nerve-muscle preparation on the alkaline side of p_H 7.4 when the nerve fiber was submerged in a buffered Ringer's solution. He found that this decrease on the alkaline side holds good for the recovery of conductivity as well as that of excitability.

As yet there is no good evidence that calcium, with its bearing on idiopathic and parathyroid deficiency tetany, has any relationship to alkalotic tetany. Although improvement of the tetanic symptoms can

12. Grant, S. B., and Goldman, A.: A Study of Forced Respiration: Experimental Production of Tetany, Am. J. Physiol. **52**:209, 1920.

13. Biederman: Electrophysiology, New York, 1898, p. 104.

14. Dale, D., and Thacker, C. R.: Hydrogen Ion Concentration Limiting Automaticity in Different Regions of the Frog's Heart, J. Physiol. **47**:493, 1914.

15. Adrian, E. D.: The Recovery Process of Excitable Tissues, J. Physiol. **54**:1, 1920.

be noted in some cases on administration of a soluble calcium salt,[6] the results do not always run favorably and improvement can, perhaps, be attributed to the well known sedative action that calcium has in reducing the excitability of the nervous system. That serum calcium is low in infantile tetany is shown in a mass of analytical data presented by Howland and Marriott,[5] and recent work by Hastings and Murray [16] shows a similar drop in the tetany following parathyroidectomy. It is as yet an open question as to the condition of the acid-base equilibrium in these diseases. It can, however, be stated with reasonable assurance that all tetanies are not alkalotic as to origin.

With the foregoing brief survey of our present knowledge of alkalosis it was thought desirable to investigate various conditions which occur clinically as possibly related to alkalosis.

METHODS

The blood samples were drawn from the median basilic vein of the arm (unless otherwise stated). A tube containing heavy paraffin oil and a small amount of dry potassium oxalate similar to the one described by Van Slyke [17] was used. A 21 gage needle was used to insure the quick flow of blood. In order to obtain the sample quickly a tourniquet was used at times to insert the needle. Determinations were usually made within one half hour after the sample was obtained.

Determination of Total Carbon Dioxid.—The total carbon dioxid was determined directly, using the Van Slyke apparatus on whole blood without equilibrating. One half c.c. 20 per cent. tartaric acid was found even better than normal lactic acid which Van Slyke and Stadie [18] had substituted for normal sulphuric acid when using whole blood. The tartaric acid dissolves the blood proteins completely so that the apparatus can be washed clean after each determination.

The hydrogen ion concentration was determined on whole blood by means of the hydrogen electrode. The electrode vessel was of the McClendon pattern but modified so that the platinum electrode could be removed as in the Clark electrode design. A tenth normal calomel electrode and connecting bridge, as previously described,[19] was used.

16. Hastings, A. B., and Murray, H. A.: Observations on Parathyroidectomized Dogs, J. Biol. Chem. **46**:233, 1921.

17. Van Slyke, D. D.: Studies of Acidosis, I. The Bicarbonate Concentration of the Blood Plasma, Its Significance, and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289, 1917.

18. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1, 1921.

19. Koehler, A. E.: A New Tenth Normal Calomel Electrode Design, J. Biol. Chem. **41**:619, 1920.

The rocking electrode, connecting bridge and calomel electrode together with the washout vessels and Weston standard cell were enclosed in a constant temperature air bath similar in design to that described by Clark [20] but being constructed of double glass walls with an air tight dead space in between. The temperaure for all determinations was 25 C. The hydrogen which was generated electrolytically was washed over concentrated sulphuric acid and ignited by means of heated platinized asbestos. The hydrogen was saturated with water at 25 C. by bubbling through wash bottles set within the air bath. A Leeds and Northrup type K potentiometer was used for the potential measurement.

EXPERIMENTAL

The Blood Reaction in Acute Fevers.—All the cases studied were those of students confined at the university infirmary. Nearly all the cases were those of a grippe-like infection with a moderately high fever during the first and sometimes the second day after entrance and a return to normal in three or four days. Dover's powders, 5 grains, acetphenetidin, 2 grains and acetylsalicylic acid, 2 grains, had been given in most cases shortly after entrance, at three hour intervals. In the majority of cases loss of appetite resulted in a very low intake of food, often only water having been taken for the preceding twenty-four hours.

TABLE 1.—Blood Reaction in Acute Fevers

Case	Day of Sample*	Temperature	Respiration	Pulse	P_H	Total CO_2	Remarks
1	2	103.4	..	...	7.513	48.3	Grippe
	5	98.0	..	...	7.394	46.6	
2	1	104.0	..	...	7.561	46.6	Grippe (no food)
	4	98.0	..	...	7.431	50.5	
3	3	103.6	24	104	7.516	41.4	Bronchopneumonia
	7	98.7	15	65	7.440	57.5	
4	1	101.2	..	...	7.459	49.8	Carbuncle on neck
	2	98.4	..	...	7.410	50.3	
5	3	103.2	..	...	7.530	47.5	Grippe
	5	98.7	..	...	7.411	52.6	
6	4	103.0	20	100	7.600	46.6	Influenza (cyanotic)
	8	98.6	14	70	7.412	54.6	
7	1	103.0	21	108	7.562	45.0	Grippe (cyanotic)
	6	98.0	..	...	7.423	53.8	
8	3	103.6	24	116	7.501	49.1	Grippe
	5	98.4	14	74	7.421	52.8	
9	2	103.7	27	110	7.557	41.8	Grippe
	4	97.9	16	72	7.413	51.7	
10	2	103.8	26	112	7.533	44.9	Grippe
	5	98.1	14	68	7.409	51.8	
11	1	103.0	23	109	7.511	48.0	Grippe
	4	98.2	15	71	7.431	52.2	
12	2	102.8	24	108	7.468	44.7	Grippe
	3	97.8	14	69	7.347	47.1	
13	1	101.6	20	105	7.451	44.8	Grippe
	3	98.0	14	73	7.423	49.0	
14	4	103.0	..	...	7.438	48.5	Influenza, alveolar abscess
	8	97.8	..	...	7.428	55.6	
15	4	102.2	26	114	7.431	44.5	Peritonitis, fatal sixth day
	5	105.0†	27	116	7.392	44.6	

* Day after onset of illness. † Rectal.

20. Clark, W. M.: The Determination of Hydrogen Ions, Baltimore, 1920.

Of twelve cases studied with a temperature of 103 F. or over, ten showed an uncompensated alkalosis. In the other two cases, one patient (Case 14), suffering from hypopituitarism, severely ill with influenza of four days' duration and suffering from an alveolar abscess, showed a p_H of 7.438; the other (Case 15), a student very ill from a peritonitis and septicemia, showed on the fourth day, 102.2 F. (axillary), a p_H of 7.431, and on the fifth day, 105.0 F. (rectal), p_H of 7.362, the sixth day being fatal. In both cases the food intake was practically nil during the period of severe illness.

In three cases with a temperature of from 101 to 102.8 F., the condition was that of compensated alkalosis.

All cases, except one, showed a drop in fixed carbon dioxid with a return to normal both of fixed carbon dioxid and p_H, on recovery. In one case (Case 2), food was withheld, except in very small quantities, for several days on account of abdominal pains and a suspected peritonitis with the resultant failure of the alkali to return to normal even though the p_H had recovered.

TABLE 2.—Effect of Starvation on Blood Reaction

	Normal		50 Hours		77 Hours		
Subject	P_H	Volume per Cent. Total CO_2	P_H	Volume per Cent. Total CO_2	P_H	Volume per Cent. Total CO_2	Remarks
C. P. C.	7.448	55.0	7.404	41.3	7.365	38.0	Complete rest
E. B. P.	7.501	58.6	7.466	48.0	7.381	43.1	Complete rest
A. E. K.	7.437	54.0	7.401	43.0	7.302	36.0	Daily work

Since most of these subjects underwent a period of starvation during high fever, a study was made on the effect of short periods of starvation on normal persons.

Effect of Starvation on Blood Reaction.—Three subjects were observed, all in good physical condition. Two were confined to complete rest in bed at the infirmary, permitted to do light reading only. The third subject, fasting for the same period, walked to and from work, a distance of several miles, and carried on a normal laboratory routine during the day.

Although the development of an acidosis on starvation has been looked on as a fact for many years, measurements of the actual blood changes have been lacking. The figures in Table 2 show that even in short periods of starvation there is a definite change in p_H toward the acid side. In all probability this drop in p_H is due to the constant elimination without replenishing of body alkali with endogenous acids, such as phosphoric and sulphuric, from protein catabolism. In a seventy-seven hour period this drop of alkali still is compensated by a

drop in carbon dioxid tension of the body fluids but a condition of uncompensated acidosis, especially in a subject not at rest, is approached.

The relation that this tendency toward an acidosis during short periods of starvation even at complete rest bears upon the observations during fever is important inasmuch as the changes are in the opposite direction, thus augmenting the difference. This tendency is perhaps a factor in "starve a fever" rationale.

To show whether or not the increase of blood p_H during an acute fever is due to the elevation of the body temperature per se or, perhaps, is due directly, or, in part, to the infection, p_H and total carbon dioxid measurements were made on subjects whose body temperature was increased by submersion in warm water.

Subject 1 experienced tingling sensation of fingers, numbness of extremities with pin prick anesthesia; saw concentric circles before the eyes at fifteen minutes; suffered mental confusion, marked quivering of eyelids when attempting to open; was unable to raise eyelids, because of

TABLE 3.—Effect of Submersion in Warm Water on Blood Reaction

Subject 1	Water Temperature, C.	Oral Temperature, F.	P_H	Total CO_2	Mm. CO_2 Tension	Pulse	Respiration
0 Min.	41	98	7.390	58.4	47.0	78	15
15 Min.	42.5	102.4	7.567	42.7	24.0	115	24
30 Min.	43.4	103.2	7.005	38.1	20.1	132	29
Subject 2							
0 Min.	41.5	98.4	7.420	51.8	41.0	76	16
15 Min.	44.8	103.8	7.521	45.4	28.0	132	24
20 Min.	45	105.3	7.365	50.9	43.0	120	27
Subject 3							
0 Min.	42.0	97.8	7.479	53.1	42.0	99	14
23 Min.	44.0	104.3	7.563	42.2	28.5	128	20
37 Min.	44.3	104.6	7.441	47.5	35.0	130	24

tetanic contraction of the rectus abdominis muscle, and was unable to straighten and unable to use limbs.

Subject 2 breathed from 8 to 10 per cent. carbon dioxid during the period from 15 to 20 minutes. The man felt weak and generally distressed, with no marked signs or symptoms. He said carbon dioxid made him feel very much better, and he got up and walked out of the tub, with quick recovery.

Subject 3 breathed carbon dioxid during the 5 minute period from 32 to 37 minutes. He felt dizzy, and very weak; had tingling of the fingers; mental confusion; numbness of extremities; flexion of wrist and metacarpophalangeal joints. He felt much better after a 15 minute period; said carbon dioxid made him feel very much better.

The acid-base balance of the blood and the various signs and symptoms of the subjects, either in natural or hot water fever, offer a picture very similar to that already discussed under forced dyspnea. In order to show this relation more clearly, a few experiments taken

from a paper soon to be published will be helpful.[20a] Medical students in good physical condition were studied in respect to normal volume respiration, normal oxygen consumption, normal carbon dioxid output, and again with respect to total carbon dioxid washed out from the whole body and the drop in total carbon dioxid per c.c. of blood after forced hyperpnea. The "Benedict Universal" metabolism apparatus was used for the determinations.

Voluntary Hyperpnea.—These subjects developed the characteristic tetanic symptoms as described by Grant and Goldman.[12]

That a similar hyperpnea with a corresponding picture of changes can be produced by a warm water fever is shown by the following experiment, similar to the first, except that in place of voluntary hyperpnea the subject was immersed in warm water and an otherwise normal resting metabolism rate measurement was made.

TABLE 4.—ACID-BASE BALANCE OF NORMAL SUBJECTS

	Subject	Normal, 10 Minute Period	Hyperpnea 10 Minute Period	Difference
Volume respiration, c.c.	C. H.	80,923	235,834	154,961
	R. S.	59,739	251,248	191,509
O_2 consumption, c.c.	C. H.	3,150	5,065	1,915
	R. S.	2,485	5,390	2,905
CO_2 output, c.c.	C. H.	2,891	5,909	3,018
	R. S.	2,158	5,507.3	3,349
Blood total CO_2 volume per cent.	C. H.	55.9	49.7	0.620
	R. S.	50.6	51.2	0.840
Ps	C. H.	7.460	7.605	0.145
	R. S.	7.451	7.657	0.206

FEVER DISCUSSION

Various investigators have from time to time dwelt on the development of an acidosis during fever until this view has become generally accepted. A careful examination of the observations on which the acidotic view has been based in the light of our present knowledge of the acid-base balance does not necessarily indicate an acidosis nor even an acidotic tendency.

The fact that the alveolar carbon dioxid tension is reduced during thermic fever, as first shown by Hill and Flack [21] has been looked on as confirming the acidotic view.[22] It will be remembered, however,

20 *a*.—Work carried on in cooperation with Dr. F. J. Hodges, Department of Physiology, University of Wisconsin.

21. Hill, L., and Flock, M.: The Influence of Hot Baths on Pulse Frequency, Blood Pressure Body Temperature, Breathing Volume, and Alveolar Tensions of Man, J. Physiol. **38**: p. lvii, 1909.

22. Barbour, H. G.: Heat Regulating Mechanism of the Body, Physiol. Rev. **1**:305, 1921.

that reduced carbon dioxid tension of the alveoli or blood alone may be diagnostic of either an acidosis or an alkalosis—the latter of the carbon dioxid deficit type as produced by hyperpnea.

Increased metabolism of the animal body during a rise in temperature has often been associated with an acidosis. Increased nitrogen elimination has been attributed to an increase in the autolytic processes due to increased H ion concentration. Mansfeld and Ernst [23] ascribe the increased protein destruction in fevers to the thyroid gland with its well known control over body oxidation. Recently, however, Du Bois,[24] in studying the basal metabolism in fever, has shown that the rate of oxidation in the animal body is directly proportional to the rise in temperature according to the temperature law of van't Hoff. Thus for every 10 degrees rise in temperature the rate of oxidation is increased approximately 2.5 times. He has shown that the basal metabolism of a fever patient is 13 per cent. higher for each degree Centigrade above normal.

TABLE 5.—EXPERIMENTAL HYPERPNEA IN A NORMAL SUBJECT PRODUCED BY SUBMERSION IN WARM WATER

	Water Temperature, C.	Oral Temperature, F.	Volume Respiration per Min. C.c.	O_2 Consumption 5 Min. per C.c.	CO_2 output 5 Min. per C.c.	Blood Total CO_2 Volume per Cent.	P_H	Pulse	Respiration per Min.
0 Min.	42.1	98.2	6.165	1.176	900	52.3	7.432	68	10.6
23 Min.	43.8	108.1	19.542	2,317	1,608	42.5	7.321	128	19-21
37 Min.	44.0	109.8	.....	.....	.....	....	.....	130	20-24

The excretion of acetone bodies during a fever does not necessarily mean an acidosis as acetone bodies have been observed in induced alkalosis, both in the alkali excess and carbon dioxid deficit types.[11] In fact, Bazett and Haldane [25] noted the excretion of acetone bodies during hot baths with all the indications of an alkalosis—diminished fall in alveolar carbon dioxid, markedly alkaline urine with high bicarbonate and no ammonia elimination.

Thus, it is readily seen that if the various experiments leading to the acidotic conception are examined for definite information as to exact measurements for an acidosis, it is, to our knowledge, not obtainable.

Haggard [10] was the first to obtain direct measurements of blood changes during immersion in hot water which enabled him to foretell

23. Mansfeld, G., and Ernst, G.: Ueber die Ursache der gesteigerten Eiweisszersetzung und Warmebildung im infektiösen Fieber, Arch. f. d. ges. Physiol. **159**:399, 1915.

24. Du Bois, E. F.: The Basal Metabolism in Fever, J. A. M. A. **77**:352 (July 30) 1921.

25. Bazett, H. C., and Haldane, J. B. S.: Some Effects of Hot Baths on Man, J. Physiol. **55**:4, 1921.

a decrease in H ion concentration. His conclusions were drawn from data obtained by determining the total carbon dioxid in blood and alveolar carbon dioxid or carbon dioxid tension of the blood by equilibrating with known carbon dioxid tensions. After a discussion of the various mechanical factors that might be responsible for the p_H change, he concludes that the carbon dioxid ratio is reduced even more by physiologic than mechanical factors.

The data presented in this paper by direct p_H measurements verify Haggard's conclusion. There is a reduction in the H_2CO_3-$NaHCO_3$ ratio with a resulting increase in p_H. In clinical fevers of the acute type the p_H may mount to 7.6, a value that may be concomitant with definite distress. The acid-base picture obtained in acute clinical fevers is practically identical with that of pure thermic fevers or can be duplicated in voluntary hyperpnea. Bazett and Haldane [25] report an increase in ventilation during hot bath from a normal of 6 to 27.3 liters per minute. These investigators believe that the respiratory center becomes more sensitive to carbon dioxid with a rise of temperature, thus resulting in a hyperpnea. Although this may be the main reason, other factors may contribute, or, in fact, offer an explanation of the foregoing mechanism. With the increase in oxidation in the body from a rise in temperature, it is altogether probable that there is a definite oxygen want in the tissues, thus resulting in an anoxemic stimulation of the respiration. An investigation being carried out in cooperation with the department of pharmacology, the results of which are soon to be published, suggests that, in spite of a blood alkalosis, the early view of the hydrogen ion stimulation of respiration during anoxemia is a possible one. This view is based on a study of the rate of transportation of carbon dioxid from cellular and intracellular fluids to the blood and upon a study of the acid-base balance during anoxemia. The introduction of this item seems important in a discussion of alkalosis inasmuch as we have no evidence as yet that blood reaction is a definite criterion of the reaction of certain tissues or a group of cells.

Alkalosis and Oxygenation of the Blood.—An increase of the carbon dioxid tension of the blood has usually been looked upon as decreasing its oxygen capacity. This relationship for normal whole blood was the result of the researches of Barcroft and his associates.[26] The investigation of Christiansen, Douglas and Haldane [27] established the fact that the concentration of the two variables $NaHCO_3$ and H_2CO_3 determines the concentration of combined oxygen. The correlation of the interdependence of these variables was shown by L. Henderson [3]

26. Barcraft, J.: The Respiratory Function of the Blood, Cambridge, 1914.

27. Christiansen, J., Douglas, C. G., and Haldane, J. S.: The Absorbtion and Dissociation of Carbon Dioxid by Human Blood, J. Physiol. **48**:244, 1914.

and can best be understood by a study of his nomogram. Thus, normally, an increase in carbonic acid is associated with a corresponding increase in sodium bicarbonate and H ion concentration so as to decrease the oxygenation of the blood. Conversely, a decrease in carbonic acid would result in increased oxygenation. It is, however, possible to conceive of a loss of carbonic acid decreasing the oxygen capacity of the blood. We would like to suggest this possibility as a factor in decreasing the oxygenation of the blood under pathologic conditions. Theoretically this condition could be brought about under certain conditions by an alkalosis due either to carbon dioxid deficit or alkali excess. A better understanding can perhaps be obtained by using concrete figures. The values have been taken from the nomogram of L. J. Henderson [8] and are only approximate.

TABLE 6.—Decreased Oxygenation Due to Alkali Excess

	P_H	H_2CO_3, Mol. per L.	$NaHCO_3$, Mol. per L.	HbO_2, per Cent.	O_2, Mm.
Normal	7.427	0.00145	0.0310	90	60
Abnormal	7.480	0.00135	0.0325	10	10

TABLE 7.—Decreased Oxygenation Due to CO_2 Deficit

	P_H	H_2CO_3, Mol. per L.	$NaHCO_3$, Mol. per L.	HbO_2, per Cent.	O_2, Mm.
Normal	7.427	0.00145	0.0310	90	60
Abnormal	7.493	0.00125	0.0312	40	50

Several cases have come under our observation which indicate that this condition comes into play clinically.

FEVER CASES

Cases 6 and 7 in Table 1 were definitely cyanotic. This cyanosis was most marked when the p_H was the highest and disappeared when the acid-base balance returned to normal. Both patients were suffering from upper respiratory infection with marked constitutional reactions. It is, of course, altogether possible that with the complication of the high fever and toxemia other factors were instrumental in producing the cyanosis.

Case 3.—Female, aged 53, had a chronic myocarditis and was suffering from cerebral thrombosis. When first seen she had marked dyspnea, Cheyne-Stokes respiration at intervals, was markedly cyanotic and irrational.

A venous blood sample was taken from her forearm showing a p_H of 7.65 and total carbon dioxid of 50.1 volume per cent. Inhalations of carbon dioxid were given from three to ten minute periods several times per day. The Cheyne-Stokes type of respiration was absent for several hours after carbon dioxid treatment. Although dyspnea was augmented at start of carbon dioxid

treatment, it was markedly decreased for periods ranging from several to twenty-four hours after the inhalations. Cyanosis was absent on days on which carbon dioxid was given and her mental condition was improved. One-half per cent. of hydrochloric acid solution with glucose and acacia was also given by the rectal drop method in from 300 to 500 c.c. amounts on two occasions.

After several days of this treatment the blood reaction had returned to normal, p_H 7.411, total carbon dioxid 53.7 volumes per cent., with her physical condition markedly improved. On cessation of treatment for forty-eight hours or more the former symptoms returned together with a marked cyanosis and alkalosis, p_H 7.649, total carbon dioxid 49.6 volumes per cent. Improvement of her physical condition was again brought about with a return of the blood reaction to normal using 10 per cent. carbon dioxid and 90 per cent. oxygen. Failure of cooperation on part of the patient made the treatments very difficult and later unwarranted. Her physical condition gradually became worse and death resulted from bronchopneumonia.

Postmortem findings by Dr. Bunting showed general arteriosclerosis, arteriosclerotic scars in kidney, cardiac dilatation, hypertrophy, chronic fibrous myocarditis, ventricular thrombi, pulmonary thrombosis and bronchopneumonia.

Case 4.—Male, aged 20, had acute arthritis, aortic and mitral insufficiency, myocarditis, chronic valvular disease. Patient was given potassium acetate, potassium citrate, 15 grains each, and sodium salicylate and sodium bicarbonate, 10 grains each, every three hours. Patient developed a very marked cyanosis and became extremely dyspneic and irrational. Respiratory rate mounted to from 50 to 60 per minute. Venous blood p_H 7.563, total carbon dioxid 58.3 volumes per cent. Two days later he was still very cyanotic; p_H 7.623; total carbon dioxid 57.1 volumes per cent. He perspired very markedly. Collected perspiration and reaction determined, p_H 4.281. The alkali administration was stopped and from 500 to 1,000 c.c. of 0.5 per cent. hydrochloric acid was given per day for three days. Cyanosis disappeared on second day, and on third day patient had a color indicating even higher oxygenation than normal, p_H 7.451, total carbon dioxid 42.8 volume per cent. With disappearance of cyanosis patient again became rational. Dyspnea slowly disappeared and patient gradually recovered.

In the few cases that have come under our observation it seems as if there is a direct correlation between the production of cyanosis and certain types of alkalosis. In view of the theoretical possibility discussed above, it is altogether probable that variations in the amounts of carbonic acid and sodium bicarbonate, both in ratio and absolute amounts, are responsible for a very definite physiologic distress due to the limiting of blood oxygenation.

It is suggested that a possible explanation of the above mechanism may be found in a disturbance of the normal shift of the chlorin ion between plasma and corpuscle. A study of the diagram of the circulation will permit a better discussion of this view. The rapid elimination of carbon dioxid from the blood thus causes a carbon dioxid deficit which, in turn, results in the passage of the sodium ion into the tissue fluids or partially in its excretion in the urine. The decreased sodium ion concentration thus prevents the transportation of the chlorin ion from the hemoglobin and so prevents the formation of oxyhemoglobin. The stimulation of the respiration from the anoxemia would result in the elimination of more carbon dioxid, thus really form-

ing a vicious cycle. The view that reduced hemoglobin ($HbCl_2$) is more basic than oxyhemoglobin (L. Henderson [3]) might also enter as a factor, inasmuch as an excess of alkali in the plasma with low carbonic acid concentration may increase the basicity of the corpuscles, thus stabilizing the hemoglobin chloride combination.[4]

CONCLUSIONS

The acid-base equilibrium is shifted toward the alkaline side during an acute clinical fever. If the fever is sufficiently high the alkalosis may result in distressing symptoms.

Fever alkalosis is very similar to that of voluntary hyperpnea or hot bath hyperpnea and is very probably due to the increased lung ventilation.

The acidotic tendency of starvation offsets, in part, the fever alkalosis. The actual change in p_H and sodium bicarbonate due to the fever is, therefore, greater than reported results.

A shift in the acid-base balance toward the alkaline side may apparently be of such a nature as to decrease the oxygenation of the blood. The concomitant occurrence of a cyanosis with a prolonged alkalosis and its disappearance upon counteracting the alkalosis has been observed clinically. Other factors operating concomitantly may, however, have been responsible for the changes.[28]

28. Since the writing of this paper a very interesting observation has been published by Morris (Anoxemia and the Increased Electrical Excitability of the Neuromyone, Brit. J. Exper. Path. **3**:101, 1922) regarding the effect of alkalosis experimentally produced in cats and dogs on the oxygenation of the blood. His experiments show that an increase in the p_H value of the blood within certain limits produced by the injection of sodium carbonate (Na_2CO_3) decreases the oxygenation of the arterial blood and still more greatly decreases the amount of oxygen given up to the tissues. Evidence is also offered that the tetany of alkalosis is an effect of the resulting anoxemia. These observations are completely confirmatory of our clinical and experimental studies.

PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

I. A STUDY OF NORMAL SUBJECTS *

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NEW YORK

INTRODUCTION

This work was originally undertaken in order to discover possible physical and chemical changes occurring in blood serum during those disturbances of water balance which result in the appearance or disappearance of edema. During the course of these studies, 172 sets of determinations have been made, and this paper presents the data from twenty-eight observations on eighteen normal subjects. The pathologic material will be discussed later. As we have failed to demonstrate any consistent changes accompanying such disturbances of water balance, this publication must be, in the main, a statistical report. We have been unable to find in the literature any previous studies of a similar nature that would demand a detailed discussion here. They are, in general, considerably less complete than this work or they present definite errors in method. The older work is well summarized in H. D. Hamburger's "Osmotischer Druck und Ionenlehre." Certain physical properties of the blood have been determined in this country by Gettler, Butterfield and others, but their studies have usually omitted a simultaneous determination of the chemical constituents.

METHODS

The following determinations were made on each serum; freezing point depression, specific conductivity at 25 C., refractive index, chlorin, HCO'_3, glucose, nonprotein nitrogen, total nitrogen, in certain cases urea and phosphorus, and more recently, sodium and potassium. All glassware was calibrated in the laboratory and the standard solutions were checked at frequent intervals. Duplicate determinations were made in practically every instance. When possible, all results are expressed in millimols per liter.

1. *Preparation of Serum.*—Blood was drawn from an arm vein by means of a well oiled (liquid petrolatum) syringe and was delivered under from 2 to 3 cm. of liquid petrolatum in 50 c.c. centrifuge tubes,

* From the Chemical Division, Medical Clinic, the Johns Hopkins University and Hospital, and from the Department of Medicine of the College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital.

thereby avoiding any exposure to air. In the collection of this blood a tourniquet was applied to the arm immediately before the vena puncture, but the period of stasis never exceeded two minutes. The blood was allowed to clot and, after separation of the clot with a glass rod, it was centrifuged. The serum was then removed at once and was almost invariably obtained without hemolysis. The time elapsing between collection of the blood and separation of the serum was about one hour. During the time involved in making the determinations, the hydrogen ion concentration of the serum did not change to exceed a range of from p_H 7.7 to 7.4.

2. *Freezing Point Depression.*—The standard Beckmann apparatus was used with a Heidenhain thermometer especially designed for cryoscopy. The usual precautions against overcooling were carefully observed, and mechanical stirring was employed. The method was checked at frequent intervals by means of tenth molar potassium chlorid and 1 per cent. sodium chlorid solutions. The freezing point of conductivity water determined the actual zero for each observation and controls were not accepted when differing by more than 0.005 C. In the process of obtaining such controls there were often several readings at great variance with the final result, and therefore, the somewhat uniform final results obtained in a series of bloods, tend to conceal these rather disturbing individual discrepancies. This fact leads us to doubt the value of cryoscopy as applied to blood serum.

3. *Electrical Conductivity.*—The conductivity was determined by means of a Kohlrausch bridge designed by Leeds and Northrup. A constant speed motor generator producing a high frequency alternating current supplied the electromotive force. Calibrated Leeds and Northrup Curtis coils furnished the variable resistances. A series of oil condensers were used to balance the capacity of the cell. The conductivity cell was of the Ostwald type requiring about 4 c.c. of serum. The cell constant, which approximated 1.5, was determined by means of a standard tenth molar potassium chlorid solution before each observation. All determinations were made in a constant temperature water bath at 25 C. and three different resistances were used in each determination. The results are expressed as specific conductivity $\times 10^{-4}$.

The effect of varying concentrations of protein upon the conductivity has been pointed out by Bugarszky and Tangl [1] and ourselves,[2] but it is impossible at present to give mathematical expression to this correction.

1. Bugarszky, St., and Tangl, F.: Arch. f. d. ges. Physiol. **72**:531, 1898.
2. Palmer, W. W.; Atchley, D. W., and Loeb, R. F.: J. Gen. Physiol. **3**: 801, 1921; **4**:585, 1922.

Normals

Date	Case	Diagnosis	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols $\frac{}{Cl}$	Millimols $\frac{}{HCO_3}$	Millimols $\frac{+}{Na}$	Millimols $\frac{+}{K}$	Millimols Glucose	Millimols Urea	N. P. N. Protein, per Cent. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
11/23/20	B.	Normal	0.542	120.2	102.0	33.3	—	—	6.5	5.7	—	7.4	7.9	17.1	P* = 0.6 millimols
11/23/20	L.	Normal	0.541	118.7	103.3	31.0	—	—	6.4	6.2	—	7.6	8.0	17.3	P = 0.6, serum turbid
12/10/20	J.	Normal	0.543	120.3	103.0	28.9	—	—	4.4	4.2	29.3	7.2	7.9	17.0	
2/15/21	Bl.	Normal	0.541	121.1	104.3	32.7	—	—	—	—	—	7.5	7.9	17.0	Serum turbid
2/24/21	H.	Normal	0.530	118.8	101.7	32.1	—	—	7.3	4.5	24.3	7.5	8.0	17.2	
3/ 1/21	F.	Normal	0.529	121.0	105.4	29.0	—	—	5.1	6.7	33.7	7.3	8.1	17.4	Serum turbid
4/ 4/21	K.	Normal	0.541	118.0	104.6	30.1	—	—	4.4	5.5	30.0	7.4	7.8	16.8	
4/ 4/21	Ke.	Normal	0.531	120.1	103.5	30.3	—	—	4.2	7.0	30.9	6.9	7.4	16.0	Slight hemolysis
4/ 6/21	R.	Normal	0.539	121.6	105.3	28.2	—	—	5.4	6.5	36.9	7.0	7.6	16.4	
4/26/21	Hib.	Normal	0.542	118.5	104.3	29.9	—	—	3.7	5.2	35.0	8.0	8.5	18.1	Serum turbid
4/26/21	I.	Normal	0.544	119.8	104.7	31.5	—	—	5.1	5.8	30.0	7.4	7.8	16.9	
4/27/21	T.	Normal	0.546	120.6	102.7	31.4	—	—	4.7	5.3	29.8	7.4	7.9	17.1	Serum turbid
4/27/21	Fe	Normal	0.548	118.3	103.0	32.0	—	—	5.1	5.0	29.5	7.8	8.2	17.6	Serum slightly turbid
4/29/21	McK.	Normal	0.549	118.2	101.7	33.3	—	—	4.6	3.8	32.6	7.7	8.3	17.8	Serum slightly turbid
1/14/21	Lo.	Normal	0.547	119.8	103.7	32.9	—	—	5.3	4.7	28.3	8.1	8.4	17.9	
2/ 5/21	Lo	Normal	0.539	120.7	102.4	35.0	—	—	4.4	4.0	35.7	7.4	8.1	17.5	
3/ 3/21	Lo.	Normal	0.551	119.6	104.2	30.1	—	—	5.1	—	32.6	7.6	8.0	17.3	
2/ 3/22	Lo.	Normal	0.530 (?)	119.8	103.6	31.7	142.2	4.5	6.3	5.0	25.0	7.8	8.4	17.9	
2/24/22	Lo.	Normal	0.522	117.6	103.7	33.1	140.9	4.6	6.2	5.3	27.0	7.8	8.1	17.4	
2/14/21	A.	Normal	0.536	118.5	104.3	30.3	—	—	4.9	4.5	24.6	7.5	7.9	17.1	
4/ 5/21	A.	Normal	0.529	120.2	104.5	30.7	—	—	4.6	7.0	30.5	7.4	7.6	16.4	
1/31/22	A.	Normal	.....	120.0	102.4	31.3	137.7	5.2	4.5	4.2	22.0	7.0	7.0	15.2	
6/23/22	A.	Normal	0.529	119.7	104.8	32.8	117.4	3.1	6.6	—	25.0	7.3	7.6	16.4	Na probably incorrect
11/24/20	P.	Normal	0.551	120.9	103.7	32.2	—	—	6.9	7.7	—	—	8.4	17.9	Serum turbid
3/ 9/21	P.	Normal	0.556	123.9	107.2	30.9	—	—	5.6	7.7	40.0	7.3	7.8	16.9	Serum turbid
4/13/21	P.	Normal	0.559	121.3	106.4	32.1	—	—	4.9	6.5	32.2	—	8.0	17.3	
2/ 1/22	P.	Normal	.....	122.8	106.6	31.5	146.5	5.1	6.2	5.3	30.9	7.7	8.5	18.2	Serum turbid
6/23/22	Be.	Normal	.....	116.5	101.4	32.8	111.2	4.5	6.2	—	25.0	8.0	8.3	17.8	Na probably incorrect

* Phosphorus in millimols.

When serum, used in our experiments, was resaturated with carbon dioxid at alveolar tension, there was no significant change in electrical conductivity (less than 0.3 per cent.). This would indicate that we were justified in ignoring the slight change in p_H due to loss of carbon dioxid.

The fact that the specific conductivity of a solution of sodium chlorid is greater than that of an equimolecular solution of sodium bicarbonate explains the greater influence of the chlorin ion on the conductivity of serum. This fact may frequently be observed in our tables.

4. *Refractive Index.*—An Abbé type of refractometer manufactured by Valentine and calibrated by the U. S. Bureau of Standards was used. The refractivity of conductivity water was determined each time, and from the differences between this figure and the index of the serum, the protein per cent. of the serum was calculated according to Robertson.[3] The refractive index is expressed as $n D \times 10^{-3}$. Temperature corrections are less than the limits of accuracy of the method and hence were omitted.

5. *Protein Per Cent.*—(*a*) Calculated from refractive index as described above.

(*b*) The protein per cent. was also determined in all cases as follows: Total nitrogen was determined in duplicate on 1 c.c. of serum by the Kjeldahl method and from this value was deducted the nonprotein nitrogen. This result, representing the protein nitrogen, was multiplied by 6.25 to determine the per cent. of protein.

6. *Nonprotein Nitrogen.*—This was determined by the method of Folin and Wu.[4]

7. *Urea.*—This was determined by Marshall's method.[5]

8. *Glucose.*—This was determined by the method of Folin and Wu.[4, 6]

9. *Carbonate Capacity.*—This was determined by the method of Van Slyke [7] in calibrated pipettes.

10. *Sodium.*—This was determined by the method of Kramer and Tisdall.[8] In our hands this method has not been entirely satisfactory in dealing with serum, although determinations on inorganic solutions were invariably correct.

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11. *Potassium.*—This was determined by the method of Kramer and Tisdall.[9]

12. *Phosphorus.*—This was determined by the method of Marriott and Haessler.[10] This method was given up because the molecular concentration of phosphorus is too low to be of significance in this work.

13. *Chlorids.*—The chlorid method was devised by us and comprises parts of the Van Slyke and Donleavy[11] and the Wetmore[12] methods. It is similar in principle to that described by Myers and Short.[13] The technic of our method is as follows: to 2 c.c. of serum are added 23 c.c. of distilled water and 15 c.c. of a saturated aqueous solution of picric acid. The solution is filtered and to a 20 c.c. aliquot are added 5 c.c. of the standard silver solution described by Wetmore.[12] The solution is agitated and allowed to stand for twenty minutes. It is then titrated without filtration using the Wetmore thiocyanate solution. The end-point is a definite change from light yellow to orange. This method agrees accurately with the Van Slyke and Donleavy method and the distillation method of Bell and Doisy.[14] All determinations were made in duplicate and titration variations of more than 0.06 c.c. were discarded.

DISCUSSION

Little generalization and no detailed statistical analysis is justified by the limited amount of data presented. It is interesting, however, to note that there are but relatively slight variations between determinations on the same and on different individuals, although the blood samples were collected without regard for time of day or diet.

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PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

II. A STUDY OF TWENTY-NINE CASES OF NEPHRITIS *

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INTRODUCTION

This paper presents fifty-two sets of observations on a series of twenty-nine cases of nephritis. The study includes five cases of acute nephritis, nine cases of uremia and fifteen cases of chronic nephritis, with and without edema. The scope of the investigation and the methods employed have been fully described in a previous communication.[1] We have found no new relationships between the laboratory findings and the clinical diagnosis, and therefore we shall omit detailed clinical descriptions.

DISCUSSION

1. *Acute Nephritis.*—These cases were typical but rather mild examples of acute nephritis with more or less hematuria. The serum analyses show no significant deviations from the normal figures except for an occasional increase in the nonprotein nitrogen. The serum chlorides were usually on the upper limit of normal. Attention may be called to the fact that the per cent. of protein in the serum is seldom below the normal in spite of the presence of some edema.

2. *Chronic Nephritis.*—A satisfactory classification of the conditions collectively known as chronic nephritis is impossible at the present time. It seems to us, however, that Widal's division of these cases emphasizing on the one hand nitrogen retention and on the other salt and water retention, affords today the most reasonable basis for clinical study. Among the seven cases of salt and water retention nephritis in our series, there are five which show a definite and unusual relationship hitherto undescribed. In all of our other cases, normal and pathological, there has been a rough but consistent relationship between the conductivity of the serum and its content of chlorin. For example, with a conductivity of 120, the chlorin content is usually about 103 millimols;

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1. Atchley, D. W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. W.: Paper I of this series.

TABLE 1.—Acute Nephritis

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N P. N. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
Dri. J.H.H. 45092	Acute nephritis	1/24/21	0.556	119.3	103.2	28.4	—	—	7.2	9.7	46.1	7.4	8.1	17.5	Edema = ±
		2/14/21	0.557	121.3	107.2	27.1	—	—	5.0	6.8	34.7	7.7	8.4	18.0	
Sc. J.H.H. 45275	Acute nephritis	1/ 4/21	0.541	124.1	107.2	28.3	—	—	4.8	7.2	44.4	6.4	6.9	15.1	Edema = +
		1/14/21	0.571	121.1	103.2	29.5	—	—	5.0	17 2	75.0	7.4	8.0	17.3	Edema = ±
		1/25/21	0.561	120.6	101.2	34.5	—	—	5.3	11 8	53.5	6.9	8.0	17.2	Edema = ±
		2/11/21	0.552	120.0	101.2	30.9	—	—	5.0	4.5	39.7	7.3	8.1	17.5	Edema = ±
Ju. J.H.H. 45080	Acute nephritis	2/10/21	0.544	120.8	102.8	26.7	—	—	4.5	5.	33.2	6.7	7.4	16.0	Edema = ±
		2/28/21	.....	121.2	103.8	31.1	—	—	4.6	—	25.0	7.1	7.5	16.2	Edema = 0
B. P.H. 53053	Acute nephritis	4/13/22	0.524	122.8	108.6	25.4	146.4	5.1	7.0	3.7	19.0	6.6	7.1	15.5	Edema = +
C. P.H. 53077	Acute nephritis	4/13/22	0.514	120.2	107.7	27.0	142.5	4.2	6.4	3.7	21.0	7.0	7.4	16.1	Edema = +

TABLE 2.—Chronic Nephritis

TABLE 2.—Chronic Nephritis

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-3}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
Gri.	Chronic nephritis	10/29/20	0.544	129.6	105.6	30.5	—	—	6.6	8.0	—	4.4	5.6	12.5	Edema = ++, P* = 0.6
J.H.H. 44662	with edema	11/ 4/20	0.533	127.7	107.3	32.9	—	—	5.7	4.8	—	4.8	5.9	13.1	Edema = ++, P = 0.5
		11/10/20	0.548	127.9	106.0	31.7	—	—	4.8	5.0	—	4.2	5.6	12.6	Edema = +, P = 0.5
		11/15/20	0.536	128.2	105.3	32.1	—	—	5.6	6.8	—	4.1	5.4	12.2	Edema = +, P = 0.8
		11/21/20	0.549	130.4	106.3	32.3	—	—	4.8	10.0	—	4.1	5.4	12.2	Edema = +, P = 0.4 serum turbid
		11/30/20	0.554	131.0	110.3	32.2	—	—	5.0	9.0	—	4.2	5.5	12.3	Edema = +, P = 0.6
		12/ 2/20	0.563	133.3	114.7	30.0	—	—	5.1	10.0	43.5	4.2	5.7	12.8	Edema = +, P = 0.4 after 10 gm. of NaCl by mouth
La.	Chronic nephritis	12/20/20	0.564	128.3	103.3	33.6	—	—	5.7	14.0	54.6	4.2	5.2	11.7	Edema = ++
J.H.H. 44835	with edema	12/27/20	0.555	128.4	104.1	31.1	—	—	6.0	11.8	50.0	4.2	5.6	12.2	Edema = ++
G.	Chronic nephritis	1/29/21	0.522	118.6	103.8	—	—	—	4.3	—	—	4.2	6.7	14.7	Edema = ++
J.H.H. 45256	with edema	2/25/21	0.533	123.6	105.1	29.9	—	—	4.9	3.3	20.5	4.3	6.5	14.2	Edema = ++, serum turbid
A.	Chronic nephritis	2/10/21	0.533	122.5	99.9	29.8	—	—	5.0	5.5	32.8	5.1	6.2	13.7	Edema = +
J.H.H. 45041	with edema														
R.	Chronic nephritis	4/ 5/21	0.550	130.7	107.9	28.3	—	—	4.7	8.2	36.6	5.4	6.2	13.7	Edema = ++
J.H.H. 45526	with edema	4/ 9/21	0.556	125.1	107.9	28.6	—	—	4.6	8.5	44.4	5.6	6.1	13.5	Edema = 0, serum slightly turbid
		4/11/21	0.549	124.4	106.9	28.7	—	—							
De.	Chronic nephritis	3/17/22	0.535	127.5	110.9	27.0	149.4	3.5	4.4	9.7	41.9	6.2	7.2	15.6	Edema = 0
P.H. 48562	with edema								6.3	—	38.0	5.0	6.1	13.5	Edema = +++, serum turbid
Ga.	Hypertension,	1/18/21	0.572	126.4	108.7	28.5	—	—	5.7	14.5	66.7	6.0	6.8	14.8	
J.H.H. 44916	chronic nephritis	1/31/21	0.535	120.9	102.7	28.3	—	—	4.9	6.8	49.2	6.0	6.4	14.0	
Ro.	Hypertension,	11/ 2/20	0.567	124.0	109.3	24.8	—	—	4.2	18.0	—	7.4	7.9	17.1	Edema = +, P = 0.6
J.H.H. 44591	chronic nephritis	11/ 5/20	0.582	125.6	110.8	24.4	—	—	8.1	20.7	—	7.3	7.5	16.3	Edema = +, P = 1.2
		11/ 9/20	0.580	122.2	104.7	27.6	—	—	6.7	17.2	—	—	8.0	17.2	P = 1.0
		11/12/20	0.569	122.1	104.8	29.8	—	—	5.6	14.5	—	7.3	8.0	17.3	P = 0.9
J.	Hypertension,	10/26/20	0.568	120.9	104.4	25.1	—	—	5.7	27.3	—	7.2	7.8	16.9	P = 1.2
J.H.H. 44471	chronic nephritis														
Se.	Chronic nephritis	3/ 7/21	0.553	120.1	102.1	25.8	—	—	5.2	21.3	70.5	5.8	6.4	14.2	Serum turbid
J.H.H. 45225															
Bu.	Chronic nephritis	3/21/21	0.532	118.9	104.1	28.5	—	—	7.4	7.2	37.0	7.0	7.2	15.7	
J.H.H. 45227															
Ma.	Chronic nephritis	2/11/21	0.526	119.9	100.1	32.7	—	—	4.2	3.2	22.5	6.2	7.1	15.4	
J.H.H. 45199		3/ 1/21	0.540	121.0	102.8	27.2	—	—	4.7	3.0	24.3	6.9	8.1	17.4	Serum turbid
Hi.	Chronic nephritis	4/13/21	0.563	117.6	112.1	12.0	—	—	5.7	24.7	90.0	7.1	7.8	16.9	
J.H.H. 45439		4/19/21	0.554	113.3	102.2	15.2	—	—	7.2	22.7	92.0	7.1	7.7	16.6	
		4/22/21	0.514	105.4	95.4	17.2	—	—	7.3	17.5	85.7	6.9	7.5	16.3	
Tr.	Chronic nephritis	4/22/21	0.536	119.7	106.6	19.4	—	—	4.7	16.8	61.2	5.3	6.0	13.3	Edema = ++
J.H.H. 45758															
Ro.	Chronic nephritis	3/15/22	0.508	114.6	102.7	27.8	136.5	4.9	5.8	—	27.9	7.9	8.0	17.2	Edema = +
P.H. 38456															

* Phosphorus in millimols.

TABLE 3.—UREMIA

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Protein, per Cent: Mg. per 100 C.c. Serum	Protein, per Cent: Kjeldahl	Protein, per Cent: Refractometer	Refractive Index	Remarks
No., J.H.H. 44396	Uremia	10/12/20	0.776	119.7	99.1	7.3	—	—	7.8	122.0	—	7.7	8.9	18.1	P* = 3.2
Su., J.H.H. 44909	Uremia	1/24/21	0.587	105.9	90.0	12.9	—	—	8.3	56.3	214.3	7.5	7.6	16.4	P = 2.3
		1/28/21	0.524	90.3	69.0	16.4	—	—	9.0	50.0	201.5	6.6	7.6	16.4	
Ku., P.H. 52996	Uremia	2/23/22	0.555	118.0	108.2	7.2	133.5	4.5	10.0	42.0	153.0	5.7	7.3	15.8	
Ke., P.H. 53317	Uremia	3/15/22	0.564	114.5	98.5	30.1	127.7	3.6	7.1	27.5	106.5	6.4	7.1	15.4	
Gr., P.H. 53551	Uremia	4/ 4/22	0.602	113.6	90.3	23.2	143.5	2.6	7.7	—	193.5	5.6	6.9	15.0	Edema = +
Co., P.H. 54009	Uremia	5/13/22	0.684	109.3	84.1	13.7	107.3	3.3	8.1	—	393.6	5.5	7.0	15.2	P = 6.1, edema = ++
W., P.H. 53725	Uremia	5/23/22	0.607	106.3	80.9	13.6	94.8	5.3	9.1	73.0	276.0	5.8	7.6	16.4	Edema = +
Noo., P.H. 54224	Uremia	6/ 2/22	0.676	122.5	108.0	6.3	129.2	5.0	9.3	65.4	—	5.9	8.2	17.6	Edema = +
Gat., P.H. 53761	Uremia	4/21/22	0.608	109.9	89.9	17.4	133.4	4.8	8.2	32.0	172.0	7.4	8.2	17.7	Edema = ++++, serum turbid

* Phosphorus in millimols.

and with a conductivity of 124, the chlorin concentration is about 109 millimols. In the five cases mentioned above the conductivity is distinctly higher than might be expected from the amount of chlorin present, whether the amount of chlorin be normal or increased, nor is this discrepancy explained by increased HCO'_3 content. For example, patient Gri. (Table 2) has a conductivity of 129.6 when the chlorin value was 105.6 millimols—a chlorin concentration within the limits of normal. In view of the work of Bugarszky and Tangl [2] and ourselves on the effect of protein concentration on electrical conductivity,[3] it was thought possible that the peculiar relationship between conductivity and chlorin concentration in these cases of nephritis might be the result of a smaller amount of protein in their sera. The case of R. (Table 2) suggests, however, that this explanation may not be sufficient in itself. In this case there intervened between the first and second observations four days during which time the conductivity-chlorid discrepancy had disappeared without change in the chlorin or protein concentrations. It is interesting to observe that during this same interval the patient's edema disappeared.

In this work we have been unable to detect any consistent physical or chemical change occurring during the process of diuresis, and we were unable to find any undescribed changes in the cases of chronic nephritis with nitrogen retention.

3. *Uremia.*—The low concentration of chlorin so frequently described in uremia was found in most of our cases. There was, however, no consistent diminution in the Na^+ content coincident with this decrease in chlorin. The general dependance of the conductivity upon the chlorin concentration is well demonstrated in Table 3.

CONCLUSIONS

1. This paper presents the results of certain physical and chemical determinations on the sera of twenty-nine cases of nephritis.

2. A hitherto undescribed relationship between electrical conductivity and chlorin concentration ("conductivity-chlorid discrepancy") has been pointed out in certain cases of salt and water retention nephritis. In these cases the conductivity is definitely greater than would be expected from the chlorin concentration.

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3. Palmer, W. W.; Atchley, D. W., and Loeb, R. F.: J. Gen. Physiol. **3**: 801, 1921; **4**:585, 1922.

PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

III. A STUDY OF MISCELLANEOUS DISEASE CONDITIONS *

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INTRODUCTION

In previous communications we have presented the results of certain physical and chemical observations on a series of normal individuals [1] and patients with renal disease.[2] In one of these papers,[1] we have described our methods in detail and have discussed the general purpose of the investigations. In this paper we have collected seventy-six sets of determinations on thirty-seven miscellaneous disease conditions. The group includes eleven cases of cardiac insufficiency with edema, six cases of diabetes mellitus, five cases of acute respiratory infection, two cases of toxaemia of pregnancy, three cases of cirrhosis hepatis with ascites, two cases of tuberculous pleurisy with effusion, two cases of diabetes insipidus, one case of cerebral hemorrhage, one case of pyloric stenosis, two cases of malignancy of the peritoneum, and one case of ascites of unknown etiology. As we have stated elsewhere,[2] case histories are omitted because no attempt is made to point out new relationships between clinical entities and the laboratory findings.

DISCUSSION

1. *Cardiac Decompensation with Edema.*—These cases are grouped together because they show more or less edema, primarily of cardiac origin. The underlying conditions responsible for the cardiac insufficiency include valvular disease, hypertension and chronic nephritis. From Table 1 it is quite apparent that we have observed no consistent physical or chemical changes in the serum accompanying the process of diuresis. For example, in case Sm., there is a considerable decrease in the freezing point depression, conductivity, and chlorin concentration with an increase in protein per cent., whereas, in Case Lo., there is a

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1. Atchley, D. W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. W.: Paper I of this series.

2. Atchley, D. W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. W.: Paper II of this series.

TABLE I.—Cardiac Decompensation with Edema

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Protein, per Cent. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
Wi. J.H.H. 44457	Hypertension, cardiac insufficiency	10/27/20	0.532	121.0	103.2	29.4	—	—	6.2	13.0	—	7.4	7.5	16.2	Edema = 0, P* = 1.9
		1/ 1/21	0.535	120.5	102.0	27.2	—	—	7.6	12.8	50.2	5.3	6.6	14.4	Edema = ++, bile tinged
		1/ 4/21	0.540	124.2	103.1	31.8	—	—	6.3	8.4	46.2	5.5	6.0	13.4	Edema = +
		1/17/21	0.523	118.4	101.2	31.4	—	—	6.6	6.5	37.8	6.3	6.8	14.8	Edema = ±
Pu. J.H.H. 44669	Hypertension, cardiac insufficiency	10/27/20	0.539	119.8	107.8	26.1	—	—	6.0	15.5	—	7.1	7.4	16.0	Edema = ++, P = 0.8
		10/30/20	0.530	119.5	98.2	38.4	—	—	5.0	6.0	—	7.2	7.2	15.6	Edema = +, P = 0.5
		11/ 6/20	0.541	117.5	102.3	33.3	—	—	5.7	—	—	7.9	8.5	18.2	Edema = 0, serum turbid, P = 0.7
		2/16/21	0.540	121.7	104.4	28.0	—	—	6.3	8.0	36.9(?)	6.4	6.9	15.1	Edema = +++
		2/18/21	0.541	121.0	98.3	35.6	—	—	4.3	6.0	37.7	6.2	7.1	15.4	Edema = ++
		3/ 8/21	0.538	119.9	104.4	32.0	—	—	5.7	—	29.5	6.9	7.6	16.5	Edema = 0
Bl. J.H.H. 44574	Aortic insufficiency	11/19/20	0.522	115.3	96.8	26.3	—	—	6.2	13.0	—	6.8	7.0	15.2	Edema = ++, P = 0.5
Sm. J.H.H. 45139	Hypertension, cardiac insufficiency	2/24/21	0.548	123.5	107.2	28.8	—	—	5.8	7.2	36.6	6.9	7.6	16.4	Edema = ++
		2/28/21	0.523	119.3	102.2	28.9	—	—	3.7	—	30.0	6.9	7.5	16.2	Edema = ±
		3/ 8/21	0.533	110.6	100.2	23.2	—	—	5.3	—	56.1	9.2	9.8	20.6	
R. J.H.H. 45224	Cardiac insufficiency	2/25/21	0.521	120.3	104.2	27.4	—	—	4.6	4.8	23.9	6.2	6.9	15.1	Edema = +
Le. J.H.H. 45336	Hypertension, cardiac insufficiency	3/ 4/21	0.550	121.5	106.1	27.9	—	—	4.6	10.7	48.0	6.6	7.0	15.2	Edema = +++
		3/ 7/21	0.536	120.1	102.2	26.9	—	—	7.7	7.5	31.4	6.3	6.7	14.6	Edema = ++
Ch. J.H.H. 45579	Cardiorenal disease	4/28/21	0.544	120.9	107.3	27.6	—	—	4.5	6.8	32.9	6.9	7.1	15.4	Edema = ++, serum bile tinged
Pa. P.H. 44216	Cardiorenal disease	3/ 7/22	0.547	125.1	113.6	23.6	137.4	4.7	7.5	13.6	55.0	6.8	6.6	14.5	Edema = ++
		3/ 8/22	0.542	125.5	114.8	24.7	142.2	4.7	7.6	13.7	42.0	6.4	7.0	15.2	Edema = ++ after theocin
		3/27/22	0.549	125.5	115.3	16.9	139.8	4.7	5.1	19.0	74.0	6.0	7.1	15.5	Edema = ++
Lo. P.H. 54287	Cardiorenal disease	6/ 5/22	0.521	114.5	95.7	25.4	105.2	3.4	7.5	—	61.0	6.1	6.8	14.9	Edema = ++++
		6/14/22	0.563	124.7	107.0	33.3	123.8	4.1	5.3	—	44.0	6.1	6.5	14.2	Edema = +
McF. P.H. 52152	Cardiac insufficiency	4/ 5/22	0.533	120.6	105.6	28.4	140.0	4.5	5.6	—	23.0	7.3	8.0	17.2	Edema = ++
		5/23/22	0.519	119.6	109.7	31.8	118.7	5.2	7.1	4.8	23.4	7.2	7.7	16.7	Edema = ± after potassium citrate by mouth
Wr. P.H. 45813	Cardiac insufficiency	5/25/22	0.466	110.5	95.7	27.0	—	3.7	6.1	—	20.0	7.2	7.2	15.7	Edema = +++

* Phosphorus in millimols.

TABLE 2.—DIABETES MELLITUS

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity × 10^{-4}	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Protein, per Cent. Mg. per 100 C.c. Serum	Kjeldahl	Refractometer	Refractive Index	Remarks
B.	Diabetes mellitus	11/13/20	0.545	116.3	98.5	29.9	—	—	11.6	6.7	—	6.1	7.8	16.8	P* = 0.6, edema ±
J.H.H. 44060		11/29/20	0.542	116.1	102.2	29.5	—	—	10.7	—	—	6.8	8.1	17.4	P = 0.4
Kl.	Hemochromatosis,	10/11/20	0.609	111.2	100.2	24.3	—	—	20.2	6.3	—	—	11.4	22.7	P = 1.3, serum lipemic
J.H.H. 44721	diabetes mellitus	11/ 1/20	0.561	119.4	93.3	31.5	—	—	13.7	3.2	—	7.4	7.2	15.7	P = 0.6
		11/29/20	0.554	117.8	97.9	29.9	—	—	15.4	17.3	—	6.2	7.2	15.7	P = 0.6
		12/17/20	0.560	109.5	94.9	22.9	—	—	16.8	4.7	—	7.2	9.7	20.6	Serum lipemic
St.	Diabetic coma	12/16/20	0.685	105.7	93.2	7.1	—	—	26.4	15.8	68.8	6.2	9.8	20.8	Serum lipemic
J.H.H. 44703															
Sa.	Diabetes mellitus	4/23/21	0.548	125.4	106.8	30.2	—	—	10.6	3.7	30.0	5.4	6.0	13.3	
J.H.H. 45437		4/28/21	—	121.6	99.7	36.6	—	—	10.9	3.7	33.1	5.9	6.6	14.5	Edema = ++
He.	Diabetes mellitus	3/20/22	0.569	119.7	104.1	21.3	136.6	3.7	17.4	—	17.6	5.8	7.4	16.0	Edema = +, serum lipemic
P.H. 53119															
Bl.	Diabetes mellitus	4/ 4/22	0.583	123.1	108.2	23.2	135.2	5.6	15.5	—	83.3	5.7	7.0	15.3	
P.H. 53556	and chronic nephritis														

* Phosphorus in millimols.

TABLE 3.—ACUTE RESPIRATORY INFECTIONS

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity × 10^{-4}	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Protein, per Cent. Mg. per 100 C.c. Serum	Kjeldahl	Refractometer	Refractive Index	Remarks
A.	Streptococcus	1/ 5/21	0.535	122.4	106.3	30.1	—	—	4.8	4.2	—	6.9	7.4	16.4	
	sore throat	2/14/21	0.536	118.5	104.3	30.3	—	—	4.9	4.5	24.6	7.5	7.9	17.1	Second observation, recovered
Z.	Pneumonia	11/14/20	0.525	113.8	95.6	28.4	—	—	6.2	8.8	42.5	7.2	7.6	16.5	P* = 0.6
J.H.H. 44657		11/16/20	0.511	113.7	96.1	29.4	—	—	5.6	7.3	—	6.5	7.1	15.4	P = 0.6
		12/ 1/20	0.541	120.3	101.5	32.7	—	—	—	7.8	—	7.2	7.6	16.4	P = 0.6
Lea.	Pneumonia	1/20/21	0.483	107.9	88.4	29.5	—	—	5.9	5.2	28.6	6.2	7.0	15.2	
J.H.H. 44931		1/25/21	0.522	110.9	88.2	33.0	—	—	8.2	8.0	46.1	6.3	7.5	16.3	Serum bile tinged
		1/28/21	0.544	112.7	94.0	30.1	—	—	8.6	12.2	57.2	7.0	7.9	17.1	Serum bile tinged
		1/31/21	0.551	114.3	95.8	29.8	—	—	9.4	12.2	43.4(?)	7.5	8.3	17.8	Serum bile tinged
Sl.	Pneumonia	3/19/21	0.510	111.0	91.1	27.8	—	—	6.6	16.2	60.7	6.1	6.7	14.7	
J.H.H. 45301		3/21/21	0.517	111.5	91.3	30.8	—	—	5.3	11.7	57.1	6.5	6.9	15.0	
McM.	Pneumonia	5/10/22	0.495	111.8	92.5	28.4	115.1	3.5	8.3	—	34.3	6.0	6.9	15.0	
P.H. 53988															

* Phosphorus in millimols.

* Phosphorus in millimols.

TABLE 4.—Toxemia of Pregnancy

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
Cl. J.H.H. 10769 (Obs.)	Eclampsia	10/21/20	0.561	120.5	107.3	13.3	—	—	13.5	5.0	—	6.4	7.9	17.1	P* = 0.8, serum Hbg. tinged, patient had just been bled, edema = ++
		10/23/20	0.508	121.3	105.6	19.6	—	—	6.4	11.7	—	5.0	5.8	13.0	P = 0.8, edema = +
		11/ 8/20	0.531	119.1	104.8	27.8	—	—	6.4	5.0	—	7.4	8.3	17.8	
Co. J.H.H. 10856 (Obs.)	Eclampsia	12/ 2/20	0.510	119.9	102.2	21.3	—	—	3.9	2.3	21.0	6.0	6.9	15.0	P = 0.6, edema = ++, patient just bled
		12/ 6/20	0.523	119.7	95.7	38.1	—	—	5.3	2.5	20.8	5.4	6.1	13.6	P = 0.6, edema = +
		12/30/20	0.520	117.5	101.4	30.0	—	—	4.6	7.0	33.0	7.6	8.2	17.7	
G. J.H.H. 10826 (Obs.)	Eclampsia and cardiac insufficiency	12/ 2/20	0.524	121.5	100.0	19.3	—	—	3.7	3.6	27.4	5.9	7.0	15.2	P = 0.6, edema = ++
		12/ 6/20	0.533	120.4	111.9	25.3	—	—	4.6	6.2	37.0	5.1	6.0	13.3	P = 0.8, edema = +
		12/ 7/20	0.542	128.5	112.9	24.0	—	—	4.9	5.8	30.0	5.3	6.1	13.5	P = 0.6, edema = +
		1/ 5/21	0.516	112.2	96.9	32.9	—	—	5.2	5.5	—	7.9	8.6	18.6	
		1/17/21	0.521	114.0	100.3	31.5	—	—	5.2	5.3	31.9	7.8	9.0	19.1	

* Phosphorus in millimols.

TABLE 5.—Cirrhosis Hepatis

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
Cl. P.H. 52949	Cirrhosis hepatis	3/12/22	0.498	113.7	100.0	27.5	124.7	4.2	7.2	—	26.0	6.8	7.3	15.8	
Ke. P.H. 50978	Cirrhosis hepatis	3/21/22	0.490	117.7	103.8	23.8	133.8	4.7	8.2	7.8	33.0	5.2	5.5	12.4	
Co. P.H. 36233	Cirrhosis hepatis	3/31/22	0.518	115.9	105.6	26.4	112.2	2.7	7.3	—	30.0	7.0	7.7	16.6	Na probably incorrect

TABLE 6.—Miscellaneous Group

Case	Diagnosis	Date	Freezing Point Depression	Specific Conductivity $\times 10^{-4}$	Millimols Cl	Millimols HCO_3	Millimols Na	Millimols K	Millimols Glucose	Millimols Urea	N. P. N. Mg. per 100 C.c. Serum	Protein, per Cent. Kjeldahl	Protein, per Cent. Refractometer	Refractive Index	Remarks
W. J.H.H. 44729	Cerebral hemorrhage	11/23/20	0.528	115.0	98.3	31.8	—	—	4.6	5.5	—	7.8	8.5	18.3	
Wa. J.H.H. 45126	Pyloric stenosis	3/ 9/21	0.524	96.9	60.5	45.9	—	—	7.9	—	88.2	8.4	8.9	19.0	
Bl. P.H. 53691	Papillary cystadenoma	4/15/22	0.529	118.2	103.2	31.1	140.0	4.3	6.3	—	16.0	7.6	7.9	17.1	
En. P.H. 53729	Carcinomatosis	4/19/22	0.509	119.4	101.8	29.0	141.7	4.3	8.6	—	—	—	7.0	15.3	
Sa. J.H.H. 45217	Diabetes insipidus	2/26/21	0.548	119.9	108.0	31.0	—	—	5.4	3.5	20.3	8.4	9.1	19.4	
		3/ 4/21	0.547	120.0	107.0	31.0	—	—	5.2	5.0	30.9	7.8	8.0	17.2	
Hi. P.H. 53197	Diabetes insipidus	3/ 8/22	0.529	119.3	103.0	33.7	138.7	4.3	5.8	3.3	20.0	7.7	8.3	17.8	Pituitrin, 2 c.c. in previous 12 hours
		3/22/22	0.530	120.3	100.3	35.3	141.7	4.0	5.1	—	19.3	7.0	7.5	16.2	
Hu. P.H. 53484	Tuberculous pleurisy	3/29/22	0.515	115.9	101.2	29.9	138 7	4.4	5.5	—	22.0	7.1	7.7	16.7	
Eg. P.H. 53614	Tuberculous pleurisy	4/15/22	0.496	113.1	100.2	26.3	129.5	5.2	5.9	—	18.0	7.0	7.1	15.5	
Ma. P.H. 46114	Ascites, cause undetermined	6/12/22	0.535	121.6	108.8	29.3	130.3	4.1	5.7	—	23.7	7.0	7.3	15.8	

marked increase in freezing point depression, conductivity, and chlorin concentration, with no change in the protein per cent. Although we have observed no consistent changes associated with diuresis, it is interesting to note that whenever there is a change in the amount of edema present, there is some coincident change in the physical or chemical properties. It has been impossible for us to predict the degree or direction of these changes. Quantitatively, however, they are very definite and usually exceed the maximal variations in a normal individual.

In the case of Pu., the changes during diuresis are quite unusual. This patient entered the hospital on two occasions separated by an interval of four months. On both admissions the patient had marked edema which disappeared rapidly following rest in bed and the administration of digitalis. The clinical improvement in both instances was accompanied by qualitatively similar changes in the blood serum. With a constant conductivity and protein per cent. there was a considerable decrease in chlorin concentration with a simultaneous increase in the HCO'_3 concentration. These variations in chlorin and HCO'_3 concentrations do not appear to be equimolecular. Each time at the completion of diuresis, the serum returned to normal.

2. *Diabetes Mellitus.*—The sera in these cases (Table 2) show no abnormalities that have not been frequently described.

3. *Acute Respiratory Infections.*—In case A (Table 3), the blood was taken at the onset of an acute streptococcus sore throat and showed no deviation from normal other than a slight increase in conductivity and chlorin concentration. The other determinations were made on patients with lobar pneumonia and show the usual changes described in this condition.

4. *Toxaemia of Pregnancy.*—Except for case Co (Table 4), no new facts are brought to light by the investigation of this group of cases. The case Co shows the same decrease in chlorin concentration and increase in a HCO'_3 concentration with practically no change in conductivity and little change in protein per cent. that was described above in case Pu of the cardiac series (Table 1). The changes in this instance, also, accompanied the loss of edema and, again, the changes were not equimolecular.

5. *Cirrhosis Hepatis.*—These three cases were classical examples of portal cirrhosis and it is interesting to note the wide spread variations in all of the determinations.

6. *Miscellaneous Group.*—No conclusions can be drawn from the analysis of isolated cases and Table 6 is presented for statistical purposes only.

BOOK REVIEW

CLINICAL MEDICINE. I. Tuesday Clinics at the Johns Hopkins Hospital. By LEWELLYS F. BARKER, M.D., LL.D., Visiting Physician to Johns Hopkins Hospital. Cloth. Price, $7 net. Pp. 617, with 66 illustrations. Philadelphia: W. B. Saunders Company, 1922.

The author states that this volume has been prepared to meet the request of many former students that a report of the work at his clinics be published. He, furthermore, presents this work as a plea in defense of the amphitheater clinic, or rather a modified type of such a clinic, in which the student participates.

A portion of the first chapter is devoted to the method of making a diagnosis. The author states that in an ordinary obscure case, in addition to the history, physical and ordinary laboratory examination, there should be included roentgenograms of dead teeth and paranasal sinuses, roentgenoscopic examination of the thorax and gastro-intestinal tract. Furthermore, the patient should be examined by the various specialists, and only after data from these various sources have been secured should the physician attempt to make a diagnosis. The question might arise as to how a student thus taught would make a diagnosis in case he engages in country practice or become a consultant.

He illustrates his method in the first clinic in a case in which the diagnosis of carcinoma of the bronchus is finally made. The author states that the history and physical examination pointed to the thorax as the seat of the trouble. The patient was given, however, a test breakfast, had roentgenograms made of teeth, sinuses, thorax, spine and the gastro-intestinal tract, and was examined by a laryngologist, a neurologist, a urologist and an orthopedist. It would appear that the diagnosis might have been arrived at much more directly and with less inconvenience and expense to the patient if a well trained internist had taken a careful history and made a physical and roentgen-ray examination of the chest. Cumbersome methods of making a diagnosis, with consequent added cost to the patient, should not be encouraged.

The author's free use of unfamiliar terms, such as "virusemia," "tabagism," "cerebritis" and "abdominous" might confuse both student and practitioner. One sentence might be quoted to illustrate this point further: "The patient has, therefore, not only an oliguric, albuminuric, cylindruric and hematuric renal disease, but also a hypochloruric, hypozoturic and hyposthenuric renal disease."

Thirty-one diseases are discussed in the clinic, including eight clinics on neurology. Dr. Barker's method of analysis of symptoms from the standpoint of pathologic physiology is highly commendable, as is also the method of teaching in which the students actively participate.

When, however, such clinics are put into book form, much of the zest is eliminated. As the author states: "No textbook and no manual can accomplish this so well as can a clinic conducted by a living human personality."

To the former student who can create a mental picture of the entire scene, no doubt this book will be read with both interest and profit. To others, however, seeking for specific information on some subject, the search for such knowledge may prove quite wearisome. Perhaps its greatest value is for the teacher of medicine, who, provided he has not already adopted this dialogue method of imparting knowledge, can profitably peruse the pages of this book.